Continuous therapy with lenalidomide in multiple myeloma

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ABSTRACT
In multiple myeloma, the depth and maintenance of response to therapy has been shown to correlate with improved survival. Therefore, treatment of residual disease after induction therapy may eradicate residual clonal plasma cells, sustain and/or deepen response and yield better outcomes. This article reviews 3 recent trials published in the *New England Journal of Medicine* investigating continuous therapy with lenalidomide. These trials each demonstrated improved outcomes for transplant-eligible and -ineligible patients treated with lenalidomide compared with placebo. While there was an increase in the rate of second primary malignancies (SPM), in an event-free survival analysis, the risk of progressive disease or death from myeloma outweighed the risk of SPM. Based on these data, continuous therapy with lenalidomide represents a new paradigm for the management of multiple myeloma patients.

PLASMA CELL BIOLOGY PRIMER AND MULTIPLE MYELOMA
Multiple myeloma is a clonal malignancy that results from an aberrant genomic event occurring during the maturation of a B cell to an antibody-producing plasma cell. Physiologically and during this process, activation-induced deaminase (AID) induces DNA double-stranded breaks (DSBs) within switch regions of the immunoglobulin heavy chain gene (IGH) of post-germinal centre B cells, allowing for IgH class switch recombination and the production of variable immunoglobulin (Ig) isotypes. However, AID can rarely introduce mutations at genes outside the Ig loci, with aberrant mutations and/or translocations that may represent the initiating event capable of pushing a plasma cell toward malignant transformation. Until recently, traditional tumour modeling (including in myeloma) had proposed that, following this initiating event, other genomic aberrations do linearly accumulate over time, eventually leading to the clinical manifestations of the disease. This model of tumour evolution implied that all clones within a tumour are linearly related to each other and homogeneous in their mutational landscape. However, genome deep-sequencing studies are now contradicting this model and revealing a more complex clonal architecture of Darwinian-like somatic evolution, where tumour progression proceeds in a branching rather than linear manner, with substantial clonal diversity and coexistence of wide genetic heterogeneity. These findings have profound therapeutic implications and have reshaped our thinking with regards to the treatment paradigms or regimen combinations required to eradicate residual clonal disease and achieve the long- elusive cure. In multiple myeloma, while the introduction of novel agents like immunomodulatory drugs (IMiDs; thalidomide, lenalidomide, and in future pomalidomide) and proteasome inhibitors (bortezomib and in future carfilzomib) into the treatment armamentarium has extended the overall survival (OS) of patients, a better understanding of the clonal dynamics along with the incorporation of triplet combinations into induction, followed by continuous suppressive therapy (as consolidation or maintenance), may further improve outcomes.

TREATMENT PATTERNS
The therapeutic approach for newly diagnosed multiple myeloma today consists of an induction phase with novel agent combinations (doublets or preferably triplets with proteasome inhibitors combined with dexamethasone and an IMiD or cyclophosphamide for 3–6 cycles) followed by an autologous stem cell transplant (ASCT) in eligible patients or a more protracted course of these drug combinations in elderly patients. Following this induction phase, some controversy remains as to whether patients should continue on therapy (with consolidation and/or maintenance) or discontinue therapy for a “treatment-free interval.” Until now, this controversy stemmed from the fact that following induction, the majority of patients eventually relapsed or developed refractory disease with no clear OS benefit from continued post-transplant or post-induction therapy.

In addition to the lack of uniformity with regards to the role of continued suppressive therapy post-induction, disparities among practices also remain about when therapy should be resumed (TNT: time to next therapy) and what defines relapse disease necessitating therapy. The International Myeloma Working Group (IMWG) subdivides relapse into...
Clinical and paraprotein relapse (see Table 1). Clinical relapse requires 1 or more of 6 indicators of increasing disease and/or end-organ damage. These include severity of bone lesions, hemoglobin levels, serum calcium and serum creatinine, and are also recognized as independent predictors of survival. In the absence of clinical relapse and according to the IMWG consensus criteria, paraprotein relapse also represents a trigger for the initiation of second-line therapy. This inclusion of paraprotein relapse as sufficient criteria for initiation of second-line salvage therapy reflects the recognition by myeloma experts that treating patients earlier (without waiting for clinical relapse) is clearly beneficial.

**THE IMPORTANCE OF A COMPLETE RESPONSE**

The IMWG consensus for defining the depth of response to therapy includes — in addition to partial response (PR) and complete response (CR) — very good partial response (VGPR) and stringent complete response (sCR), 2 additional categories that highlight the importance of eradicating minimal residual disease (MRD). These 2 new categories include immuno-phenotypic CR (>4-colour flow cytometry) and molecular CR (allele-specific oligonucleotide PCR) with clonal plasma cell detection sensitivities of $10^{-5} = 1/10^5 = 1/100,000$ and $10^{-6}$ respectively. In a long-term survival analysis of patients with multiple myeloma, after 17 years' followup, 35% of patients in the CR group were alive, in contrast to 11% of patients achieving less than CR. Therefore, achievement of a CR post-transplant or post-induction is essential for improved survival outcomes, but perhaps more important is maintaining this CR and potentially even deepening the response to sCR, immunophenotypic CR or molecular CR (see Figure 1).}

**THE EMERGENCE OF RESISTANT CLONES**

Multiple myeloma is composed of several genomically distinct subclones coexisting in varying proportions and dynamically competing for the bone marrow stromal niches. While one dominant clone may be eliminated with induction therapy and ASCT, residual minor clones are likely to expand with this resetting of the clonal dynamics and hence herald a rapid clinical relapse. Furthermore, the incidence of deletion 17p13, which contains the TP53 locus, increases with every relapse, with rates reaching 80% in plasma cell leukemia compared to ~10% in newly diagnosed disease. These observations suggest that continuous suppressive therapy may not only delay disease relapse by eradicating residual clones, but also arguably delay the emergence of deletion 17p13. While comparative sequential cytogenetic and genomics studies to support this latter argument are lacking, clear analogy may be drawn from follicular lymphoma trials where the use of continuous rituximab is demonstrated to significantly improve progression-free survival (PFS) and OS. This improvement in survival outcomes in low-grade lymphomas with maintenance rituximab results from the delay in clonal transformation to more aggressive large-cell lymphomas.

**CONTINUOUS SUPPRESSIVE THERAPY WITH LENALIDOMIDE**

Based on the premise that 1) the depth of response is associated with improved survival (CR better than sCR), 2) a sustained CR is associated with better survival outcomes, and 3) eradication of residual clones may delay disease relapse and hence defer the emergence of del17p13, it seems logical to adopt long-term suppressive or maintenance therapy in multiple myeloma. Recently, 3 trials investigating the use of continuous therapy with lenalidomide were published in the New England Journal of Medicine (see Table 2).

**CALGB 100104**

In the CALGB 100104 trial, patients who had achieved stable disease or better 100 days after undergoing ASCT were randomized to placebo (n=229) or lenalidomide (starting dose 10 mg/day) (n=231) until disease progression. The study was unblinded at a median followup of 18 months due to significantly longer time-to-progression (TTP) in the lenalidomide group; 20% of patients in the lenalidomide group and 44% of patients in the placebo group had progressive disease (p<0.001) (see Figure 2A). Patients in the placebo group without progressive disease were allowed to cross over to lenalidomide at unblinding (67% of those patients crossing over).

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**Table 1. International Myeloma Working Group (IMWG) criteria for defining relapse.**

<table>
<thead>
<tr>
<th>Clinical relapse</th>
<th>Paraprotein relapse (Biochemical relapse)</th>
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<tr>
<td>One or more of the following indicators:</td>
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<tr>
<td>- Development of any new soft-tissue plasmacytomas or bone lesions on skeletal survey, MRI or other imaging</td>
<td>- Doubling of the M protein component to 2 consecutive measurements separated by ≥2 months</td>
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<tr>
<td>- Define 1 in size of existing plasmacytomas or bone lesions</td>
<td>- T in the absolute levels of serum M protein by ≥1 g/dL</td>
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<tr>
<td>- Hypercalcemia (≥11.5 mg/dL; &gt;2.875 mM/L)</td>
<td>- T in the absolute levels of urine M protein by ≥500 mg/24 hours</td>
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<tr>
<td>- ↓ in Hb by ≥2 g/dL (1.25 mM) or to &lt;10 g/dL</td>
<td>- T in the absolute levels of involved FLC level by ≥20 mg/dL (plus an abnormal FLC ratio) in 2 consecutive measurements separated by ≥2 months</td>
</tr>
<tr>
<td>- ↑ in sCr by ≥2 mg/dL (≥177 mM/L)</td>
<td></td>
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<tr>
<td>- Hyperviscosity</td>
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Note: "↑" indicates an increase, "↓" indicates a decrease, and "-" indicates no change. Clinical relapse is defined as 50% (and at least 1 cm) increase as measured serially by the sum of the products of the cross-diameters of the measurable lesion; Hb: hemoglobin; FLC: free light chain; M protein: monoclonal protein; MRD: minimal residual disease.
eligible crossed over). Importantly, the lenalidomide group had significantly improved OS; at a median followup of 3 years, 85% of those in the lenalidomide group and 77% of those in the placebo group were alive (see Figure 2B). Of interest, patients in the lenalidomide maintenance arm consistently demonstrated better outcomes regardless of whether they received lenalidomide or not in their induction regimen. In fact, patients receiving lenalidomide-based induction demonstrated the most benefit from lenalidomide maintenance. While this observation could be attributed to the fact that patients who did not respond to induction lenalidomide therapy were excluded from this trial, it nevertheless suggests that patients who respond to lenalidomide induction will also benefit from it when given as maintenance therapy post-induction.

The lenalidomide group demonstrated longer median TTP regardless of whether they had achieved CR, although achievement of CR improved outcomes within the groups. At unblinding, the median TTP had not been reached in the lenalidomide CR group, was 37 months in the lenalidomide non-CR group, 35 months in the placebo CR group, and 20 months in the placebo non-CR group.

In the lenalidomide group, 10% of patients discontinued therapy due to adverse events, compared with 1% of patients in the placebo group, before crossover. In addition, a slightly increased risk of second primary malignancy (SPM) was seen in the lenalidomide group (8% of lenalidomide-treated patients versus 3% of placebo-treated patients). Some of the most common adverse events were hematologic (e.g., neutropenia, thrombocytopenia, etc.), which, in most cases, are manageable toxicities.

**IFM 2005-02**

The IFM 2005-02 trial investigated continuous lenalidomide therapy (10 mg/day for the first 3 months, increased to 15 mg/day if tolerated; n=307) vs placebo (n=307) in patients with non-progressive disease following ASCT, until disease progression. Of note, in this trial most patients (577 of 614) received 2 cycles of consolidation therapy with 25 mg lenalidomide after randomization to lenalidomide maintenance or placebo. Continuous lenalidomide therapy significantly increased median PFS (41 months vs 23 months for placebo; p<0.001) (see Figure 2C). The study was unblinded when the prespecified level of significance for PFS was reached. Patients continued on therapy without crossover and, 6 months after study unblinding, lenalidomide therapy was stopped due to the observation of an increased incidence of SPM (3.1/100 patient-years in the lenalidomide group vs 1.2/100 patient-years in the placebo group).

In contrast to the CALGB trial, and despite a large improvement in PFS, there was no difference in OS between the two groups at a median followup of 45 months. There are a number of differences between the IFM 2005-02 and the CALGB 100104 trial that may have contributed to the differences in OS findings (Table 3). Among these, early discontinuation of lenalidomide therapy in the IFM trial (due to SPMs), the use of 2 cycles of lenalidomide consolidation in both arms of the IFM trial, and a large imbalance in the proportion of patients with high-risk disease in the lenalidomide arm (21%) vs placebo (12%) all surely played a role in the lack of OS benefit in the IFM trial. It should also be noted that OS was not a primary endpoint in either study, nor were they powered to detect a difference in OS.

More patients in the lenalidomide group than the placebo group discontinued due to adverse events (27% vs 15%). As with the CALGB 100104 trial, some of the most common adverse events were hematologic in nature.

**MM-015**

In the MM-015 trial, patients with newly diagnosed multiple myeloma who were ineligible for ASCT were randomized to MP (melphalan-prednisone; n=154), MPR (melphalan-prednisone-lenalidomide; n=153) or MPR-R (melphalan-prednisone-lenalidomide followed by continuous lenalidomide until disease progression; n=152). The 3-year OS was not significantly different between the 3 groups; however, the MPR-R group demonstrated significantly longer PFS (median 31 months) compared with MPR (median 14 months) or MP (13 months) (see Fig. 2D). There was no significant difference between the MPR and MP group, suggesting that using a novel agent for induction therapy is not sufficient to improve outcomes. Together with data from studies of continuous bortezomib therapy in patients ineligible for ASCT, this trial indicates that continuous therapy is equally useful in elderly patients.

The most frequent adverse events were hematologic in nature. The rate of SPM was 7% in the MPR-R and MPR groups, 3% in the MP group.

**SECOND PRIMARY MALIGNANCY**

In all 3 studies, lenalidomide-treated groups demonstrated higher rates of SPM than placebo or control groups. But in a reanalysis of the survival data with SPM censored as an event along with progressive disease or death, the median event-free survival (EFS) remained significantly longer in favour of the...
lenalidomide maintenance groups.1-3 Of note, the lifetime risk of therapy-related myelodysplastic syndrome (MDS) or acute myeloid leukemia with high-dose chemotherapy and ASCT is 5%, even larger than that observed with lenalidomide in some studies.27 While current studies indicate that patients with plasma cell dyscrasias, including monoclonal gammapathy of undetermined significance (MGUS), have a higher risk of MDS as well as other malignancies, further research into this area will help uncover which patients are at higher risk of developing secondary malignancies (due to prior therapy, cytogenetics, etc.) and allow a better distinction between host- or therapy-related risk factors.

UNANSWERED QUESTIONS
What is the optimal duration of continuous therapy?
The optimal duration of maintenance therapy with lenalidomide in multiple myeloma is yet to be defined. In the IFM 2005-02 trial, therapy was discontinued at a median of 24 months.13 However, the best results with continuous therapy were seen in the CALGB 100104 trial, which demonstrated an OS advantage, despite crossover of patients in the placebo arm. In this trial, therapy was continued until disease progression or intolerable toxicity. It would therefore appear that maintenance therapy with lenalidomide until disease progression is the optimal duration, but randomized trials are still needed to fully answer this question.

Does consolidation therapy obviate the need for continuous therapy?
A study by the Italian Myeloma Network comparing bortezomib-thalidomide-dexamethasone consolidation to thalidomide-dexamethasone consolidation showed that more intensive consolidation improves outcomes.28 However, in the IFM 2005-02 trial, all patients received 2 cycles of lenalidomide consolidation, yet the lenalidomide group still demonstrated a PFS benefit, suggesting that consolidation alone, at least when given as 2 cycles of 25 mg of lenalidomide, is not sufficient to improve PFS.2 Of interest, however, in subset analysis of the IFM trial, patients receiving tandem ASCT did not seem to benefit from lenalidomide maintenance as much as those treated with a single ASCT.2

Is continuous therapy for everyone?
In the IFM 2005-02 trial, a PFS benefit was demonstrated across all patient subgroups (age, International Staging System stage, sex, Ig isotype, number of transplants, cytogenetics, CR at the time of randomization).2 In the CALGB 100104 trial, the lenalidomide group demonstrated improved TTP regardless of whether or not patients had achieved a CR.2 In light of the intraclonal heterogeneity in this disease, a theoretical concern arises that such a strategy may eradicate the indolent clone, resetting clonal dynamics by eliminating competitive populating pressure for the bone marrow niches and facilitating the
selection of pre-existing more-aggressive clones, which will ultimately impair post-relapse survival. If true, such a model of altered selective pressures favours a maintenance approach where doublet or triplet combinations or sequential alternation of different classes of drugs are used. Of note, subset analysis of the IFM trial showed that patients with or without del13q benefited equally from lenalidomide maintenance. Future studies dedicated to patients with high-risk cytogenetics (in particular del17p and t(4;14)) will be required.

**What is the optimal continuous therapy regimen?**

A number of studies of continuous thalidomide therapy have demonstrated significant improvements in PFS and OS, similar to the 3 continuous lenalidomide therapy trials. Trials with continuous bortezomib or bortezomib-thalidomide have also demonstrated improvements in PFS.

**WHICH REGIMEN IS BEST?**

Theoretically, the optimal continuous therapy regimen shall be highly effective, equally capable of eradicating dominant and minor clones, prevent the emergence of resistant subclones and be void of toxicity, while being convenient for patients — i.e. fully oral. The results of future randomized trials will help to determine what the optimal regimen is. For now at least, continuous therapy with lenalidomide appears to benefit multiple myeloma patients and should be considered for integration into treatment paradigms.

**References**

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7. Poon ML, Chng WJ. Is complete remission an important therapeutic aim in multiple myeloma? *Cancer Ther* 2008 May;8:275-84.