The efficacy of thalidomide at doses as low as 50 mg every other day was first reported at the VII International Multiple Myeloma Workshop in Stockholm, Sweden, in September 1999. This article discusses the duration of responses with low-dose thalidomide and the subsequent efficacy with thalidomide combination approaches. The median effective dose of thalidomide was 200 mg/d. Thalidomide’s mechanism of action, particularly its effects on macrophages, is described. Current approaches to single-agent and combination therapy are presented.

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DURING 1998, a phase II study was initiated in Little Rock, AR, using a rapid-dose (every 2 weeks) escalation protocol with doses of 200 mg/d to 800 mg/d of thalidomide. Because responses in the Little Rock study occurred early and dose escalation significantly increased toxicity, it was elected to conduct a study to evaluate the efficacy of low-dose thalidomide.

LOW-DOSE THALIDOMIDE PHASE II STUDY

Low-dose thalidomide was evaluated for induction and maintenance in patients with relapsing and refractory myeloma. Remission duration and survival were assessed with over 3 years of follow-up in patients with relapsing disease after both transplant and standard-dose chemotherapy. Patients were treated with thalidomide 50 mg/d as a starting dose. Dose escalation was based on lack of response. An adequate trial was 8 weeks with M-protein monitoring and dose adjustment (ie, 50, 100, or 200 mg) every 16 to 28 days. In the initial phase of the study, 36 patients were accrued and evaluated for response and toxicity. Six patients had more than 75% regression (complete remission); three patients had between 50% and 75% regression (partial remission), and seven patients had between 25% and 50% regression (< partial remission), producing an overall remission rate of 44% (Table 1). The remaining patients had progressive disease and/or discontinued thalidomide prior to 8 weeks. Of the nine patients (25%) with at least 50% regression, all (100%) were in remission at 6 months; six patients (67%) remained in remission at 18 months, but only two patients (22%) were still in remission at 2 years (Fig 1). Both patients still in remission over 3 months had the lowest doses (50 mg daily and 50 mg every other day). Conversely, only one responding patient has died, and that patient required the highest dose of thalidomide. In this study, the higher-dose patients relapsed sooner. It also was noted that response was more likely with light chain subtype disease (P < .01). Patients having between 25% and 50% regression (ie, < partial remission), and those progressing on thalidomide alone, had dexamethasone 40 mg/d for 4 days twice per month added to their regimen. Of the seven < partial remission patients, three (43%) responded for 6, 15, and 23 or more months. The low doses of thalidomide were generally well-tolerated. However, progressive peripheral neuropathy was the major long-term toxicity. The thalidomide dosage was reduced to 50 mg every other day, less frequently or even discontinued, because all patients ultimately developed at least grade I-II neurotoxicity. The neurotoxicity was predominately peripheral neuropathy with progressive numbness and tingling; only rarely was the neuropathy painful in this study.

LOW-DOSE THALIDOMIDE AND OTHER DISEASES

Responses to very low doses of thalidomide should not be surprising, because thalidomide has been used to treat a wide variety of diseases at doses of 25 mg to 300 mg/d. The majority of maximum responses have been observed in the 100-mg to 300-mg dose range, with a median effective dose of approximately 200 mg. Additionally, sustained response upon discontinuing thalid-
omide has been observed with the use of thalidomide in other diseases. For example, in rheumatoid arthritis, responses have been reported to last from 8 months to 6 years after thalidomide has been discontinued. The role of thalidomide maintenance remains to be studied for multiple myeloma. However, in this phase II trial with low-dose thalidomide, relapse occurred off-drug and was recaptured by restarting the drug. Remissions of more than 6 months off thalidomide maintenance were observed.

The effectiveness of very low doses of thalidomide strongly suggests an anti-inflammatory and/or immunomodulatory mechanism of action. At low doses, thalidomide has selective inhibitory effects on macrophage-derived tumor necrosis factor-α (TNF-α) and interleukin-12 (IL-12). Partial inhibition of TNF-α and IL-12 production is preferable to total inhibition because TNF-α plays a pivotal role in host resistance, and IL-12 is required for viral-specific, natural killer-cell–mediated immunity. This explains the paradoxical effects in human immunodeficiency virus patients in whom thalidomide may directly inhibit replication of human immunodeficiency virus, but also suppresses the required IL-12–mediated immune response to human immunodeficiency virus. Precise thalidomide effects that are most relevant to anti-myeloma efficacy are controversial. However, the selective binding of thalidomide to α1-acid glycoprotein (AAG) may be involved in its inhibition of TNF-α production. AAG, also known as orosomucoid, is an acute-phase protein produced in soluble form by hepatocytes and monocytes/macrophages. AAG also has profound effects on platelet aggregation and blood clot formation. This may account for recent reports of hypercoagulability with thalidomide use, especially combined with chemotherapy. However, this is rarely observed with low doses of thalidomide administered alone or in combination.

**ROLE OF NUCLEAR FACTOR-κB**

Decreased nuclear factor (NF)-κB levels and binding activity is most likely the ultimate critical effect. The NF-κB cascade is central to the activation of monocyte/macrophages regarding cytokine production, adhesion molecule expression, and viral activation. The proteasome activity and NF-κB activation in monocytes/macrophages may also be the target for PS-341, which has recently shown dramatic benefit in relapsing and refractory myeloma. In addition, monocyte/macrophage cells are known to be important, if not essential, for active myeloma cell growth. Another macrophage-derived factor of potential interest and importance is migration inhibitory factor. Migration inhibitory factor is also triggered...
by NF-κB and has several properties, including promotion of neoangiogenesis, inhibition of p53 tumor-suppression activity, and antagonism to glucocorticoid anti-inflammatory effects. In summary, thalidomide can affect TNF via either of the two pathways highlighted in Fig 2. The critical effect is on NF-κB and it is the central player, which in turn affects numerous cytokines, TNF-α, and IL-12. Genes regulated by NF-κB and pertinent to thalidomide are listed in Table 2. It has been shown that NF-κB and viruses manifest reciprocal transactivation.

**EARLY STUDIES WITH STEALTH-ADAPTED VIRUSES**

Stealth-adapted viruses have been studied in collaboration with the Center for Complex Infections Disease, evidence of stealth-adapted virus has been documented in cultures from approximately 70% of patients with active myeloma. The cultures show shedding of whole virus particles and smaller viral particles in part because there is a defect in the formation of the viral lipid protein coat. The stealth virus particles show strong homology with simian cytomegalovirus, with the exception that they are about half the size of normal

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**Table 2. Genes Regulated by Nuclear Factor-κB**

<table>
<thead>
<tr>
<th>Cytokines</th>
<th>Cell Adhesion</th>
<th>Other</th>
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<tbody>
<tr>
<td>IL-1</td>
<td>V Cam-1</td>
<td>Chemokines (eg: MIP-1α, CCR5)</td>
</tr>
<tr>
<td>IL-2</td>
<td></td>
<td>C-myc</td>
</tr>
<tr>
<td>IL-6</td>
<td></td>
<td>K-light chain</td>
</tr>
<tr>
<td>IL-8</td>
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<td>IL-12</td>
<td>ICAM-1</td>
<td>Viral transactivation</td>
</tr>
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<td>IL-15</td>
<td>E-selectin</td>
<td></td>
</tr>
<tr>
<td>IL-18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TNF</td>
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</tbody>
</table>

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**Fig 2.** Major nuclear transcription pathways. IL, interleukin; JAK, Janus kinase; STAT, signal transduction and activators of transcription; JNK, Jun N-terminal kinase; MEKK, MEK (MAPK, or ERK, kinase) kinase.
cytomegalovirus and has deletion of several critical T-cell stimulatory factors. An important feature of this virus is that it has the capacity to produce chemokines such as MIP-1α (a known important osteoclast stimulating factor), to constitutively activate NF-κB, and to trigger abnormal lipid biosynthesis involving the mevalonic acid pathway. However, these viruses do accumulate and proliferate in macrophages such as those present in the bone marrow microenvironment. Myeloma cells grown in colony culture from fresh bone marrow samples grow consistently around accessory cells, most frequently macrophages. Therefore, an important unresolved question is whether or not it is more important to inhibit NF-κB in the macrophage or in the myeloma cell. Use of array technology for genomic and proteomic studies may be necessary to evaluate both the macrophage as well as myeloma cells. The macrophage may be an important target for therapy. If stealth-adapted viruses prove important in pathogenesis, then antiviral therapy may provide added synergistic benefit.

**SUMMARY OF RESULTS WITH THALIDOMIDE**

Thalidomide as monotherapy has a 25% to 35% response rate in relapsing patients and 5% to 10% higher response rate in front-line therapy. Substantial synergistic effects occur using thalidomide at doses of 50 mg/d when pulse dexamethasone has been added. A compilation of response rates from Cedars-Sinai (Los Angeles, CA) using this low-dose thalidomide approach, and the Mayo Clinic (Rochester, MN, and M. D. Anderson (Houston, TX), using thalidomide at 200 to 400 mg/d, are shown in Table 3. Comparative studies are necessary to assess relative efficacy of low doses for response and remission duration. Adverse effects associated with the thalidomide/dexamethasone combination are tolerable, but thrombophlebitis and skin reactions may occur. Skin reactions that occur with thalidomide appear to be dose-related at 400 mg (or higher), but rarely occur with 200 mg. Thalidomide at 50 mg/d to 200 mg/d combined with dexamethasone has a very low incidence of thrombophlebitic and skin problems. Combining thalidomide/dexamethasone with clarithromycin (BLT-D) to create a three-drug combination also has potential advantages. In vitro and clinical synergy has been reported. A high response rate (> 80%) in patients with relapsing/refractory disease has been reported. However, cases of thrombophlebitic and cardiovascular complications have been reported with the three-drug combination and require careful clinical management. Comparative studies are urgently required to assess efficacy and toxicity.

The remarkable efficacy with low doses of thalidomide offers great benefit for patients with acceptable toxicity. Future studies will help define the optimum dosage of thalidomide alone and in combination.

**REFERENCES**


7. Makonkaweyoon S, Limson-Pobre RN, Moreira AL, et al: Thalidomide inhibits the replication of human immunode-

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**Table 3. Updated Response Rate Data**

<table>
<thead>
<tr>
<th></th>
<th>Relapse</th>
<th>Frontline</th>
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<tbody>
<tr>
<td>Thalidomide monotherapy</td>
<td>25% to 35%</td>
<td>35% to 45%</td>
</tr>
<tr>
<td>Thalidomide/dexamethasone</td>
<td>Cedars* 59%</td>
<td>76%</td>
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<tr>
<td>Thalidomide/dexamethasone</td>
<td>Mayo† –</td>
<td>64%</td>
</tr>
<tr>
<td>Thalidomide/dexamethasone</td>
<td>MDA‡ 65%</td>
<td>78%</td>
</tr>
</tbody>
</table>

* Cedars-Sinai Comprehensive Cancer Center, Los Angeles, CA.
† Mayo Clinic, Rochester, MN.
‡ M. D. Anderson Cancer Center, Houston, TX.
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25. Bucala R: The effects of the signaling molecule MIF are quite well understood, but how it works remains a mystery: Some of the pathways behind its activity have now been revealed—with surprising results. Nature 408:146-147, 2000