FEATURE ARTICLE

Advances in Oral Therapy in the Treatment of Multiple Myeloma

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Conventional IV chemotherapy regimens used for induction chemotherapy or salvage therapy in the treatment of multiple myeloma (MM) are cumbersome, with a negative impact on patient quality of life. A number of new oral drugs, including immunomodulatory agents such as thalidomide and lenalidomide, have demonstrated potent antimyeloma activity in relapsed and refractory as well as newly diagnosed MM. Clinically, response rates of 56%–72% have been reported with the combination of thalidomide and dexamethasone in patients with newly diagnosed disease; however, the combination is associated with a higher incidence of side effects, including constipation, somnolence, peripheral neuropathy, and thromboembolic complications. In contrast, preliminary safety and efficacy data from clinical studies of lenalidomide show promise. Response rates as high as 83% have been reported in patients with newly diagnosed MM, and the most common adverse event is manageable myelosuppression, which is reversible with dose reduction. Lenalidomide has different toxicities than thalidomide, exhibiting greater myelosuppression but virtually no constipation, somnolence, or peripheral neuropathy. Oncology nurses play a key role in monitoring patients for side effects and pain control and educating them about emerging treatment options. This article reviews the nursing experience with oral agents in the treatment of MM.

Multiple myeloma (MM) is the second most common hematologic malignancy in the United States and accounts for an estimated 14% of all newly diagnosed hematologic malignancies (American Cancer Society, 2005). Standard therapy has included melphalan and prednisone; vincristine, doxorubicin, and dexamethasone (VAD); or single-agent dexamethasone (Kyle & Rajkumar, 2004). Although the response rate with VAD as initial therapy is slightly better than that with melphalan and prednisone (Myeloma Trialists’ Collaborative Group, 1998), VAD appears to offer no survival advantage over melphalan and prednisone. In addition, IV combination chemotherapy regimens have several disadvantages, including the need to establish a central venous catheter, risk of catheter-related infections, and potential cardiac toxicity (Alexanian, Barlogie, & Tucker, 1990; Hideshima & Anderson, 2002).

Some of the newer agents, such as proteasome inhibitor bortezomib, require IV administration (Munshi, 2004). Others, including thalidomide, lenalidomide, specific inhibitors of farnesyl transferase, histone deacetylase, and vascular endothelial growth factor (VEGF), are administered orally. The oral agents have demonstrated potent activity in MM in vitro (Harousseau, Shaughnessy, & Richardson, 2004; Munshi) and potent in vivo antmyeloma activity in all categories of MM. However, the oral agents’ distinctive tolerability profiles may impact their use in different patient populations. This article will discuss clinical experiences and nursing implications of oral agents in the treatment of MM.
as well as relapsed and refractory disease (Alexanian, Barlogie, & Dixon, 1986; Alexanian, Dimopoulos, Delasalle, & Barlogie, 1992). High-dose dexamethasone therapy was effective in about 30%–40% of patients with resistant MM (Alexanian et al., 1986; Friedenberg et al., 1991). However, moderate to severe side effects occurred in 55% of patients (Friedenberg et al.), suggesting that the regimen is poorly tolerated, thus limiting its use. Intermittent, or pulsed, high-dose dexamethasone (40 mg by mouth, four days on, four days off) is currently used. Although associated with toxicity, pulsed high-dose dexamethasone induces rapid responses in patients with relapsed and refractory as well as newly diagnosed MM; a response rate of 40% and an overall survival similar to that with VAD therapy have been observed (Alexanian et al., 1992; Tiplady & Summerfield, 2000). The National Comprehensive Cancer Network (NCCN, 2006) recommended the use of dexamethasone as primary therapy in patients with MM prior to autologous stem cell transplantation.

**Thalidomide**

After almost two decades without an advance in the treatment of MM, thalidomide emerged as a potentially effective oral therapy based on its known antiangiogenic and immunomodulatory properties and the observation of increased angiogenesis in the bone marrow of patients with MM (Bartlett, Dredge, & Dalgleish, 2004; D’Amato, Loughnan, Flynn, & Folkman, 1994). Most clinical trials of thalidomide monotherapy have demonstrated activity (objective response, defined as a reduction in paraprotein levels) in one-third of patients with relapsed and refractory MM (Barlogie et al., 2001; Hus et al., 2001; Kumar et al., 2003; Richardson et al., 2004; Singhal et al., 1999) and newly diagnosed MM (Rajkumar et al., 2003; Weber, Rankin, Gavino, Delasalle, & Alexanian, 2003).

The combination of thalidomide and dexamethasone (thal/dex) also has been evaluated in the treatment of relapsed and refractory and newly diagnosed MM. In the relapsed and refractory setting, objective responses to thal/dex (defined as a reduction in paraprotein levels) have been reported in 47%–60% of patients (Anagnostopoulos, Weber, Rankin, Delasalle, & Alexanian, 2003; Bernardeschi et al., 2004; Palumbo et al., 2001, 2004). The addition of dexamethasone to thalidomide has reduced median time to response to four months (range = 0.5–21 months), with 33% of the maximal responses occurring during the first two months of therapy (Palumbo et al., 2001, 2004). In a comparison of thal/dex and conventional VAD chemotherapy in patients with relapsed and refractory disease, thal/dex provided superior median progression-free survival (17 months with thal/dex versus 11 months with VAD; p = 0.0024) and three-year survival (60% with thal/dex versus 26% with VAD, p = 0.0016) (Palumbo et al., 2004).

In patients with newly diagnosed MM, thal/dex has resulted in a response rate of 64%–72% (Cavo et al., 2004; Rajkumar, Blood, Vesole, Shepard, & Greipp, 2004; Rajkumar et al., 2002; Weber et al., 2003). Median time to remission is faster with thal/dex than with single-agent thalidomide (0.7 months with thal/dex versus 4.2 months with thalidomide alone) (Weber et al.). Interim analysis of data from a phase III, randomized study comparing the safety and efficacy of thal/dex with that of dexamethasone alone in patients with newly diagnosed MM showed higher response rates (measured as a 50% or greater reduction in paraprotein) with thal/dex (80% with thal/dex versus 53% with dexamethasone alone; p = 0.0023) (Rajkumar et al., 2004). Thal/dex also has been shown to be superior to VAD as induction therapy for patients undergoing autologous transplantation (Cavo et al., 2005). In a retrospective analysis, patients treated with thal/dex exhibited a higher response rate (76% with thal/dex versus 52% with VAD, p = 0.0004) and a greater reduction in myeloma cell mass (p = 0.02 for IgG myelomas and p = 0.05 for IgA myelomas) compared with those treated with VAD (Cavo et al., 2005). Although the findings need confirmation, the use of thal/dex may be a suitable alternative to VAD and to single-agent dexamethasone as first-line therapy for patients with newly diagnosed MM who are eligible for autologous transplantation. The use of thal/dex as consolidation therapy also has been shown to be effective in patients with persistent partial response after myeloblastic therapy, with more than half of patients achieving a 90% or more reduction in paraprotein (Alexanian, Weber, Giralt, & Delasalle, 2002). Based on clinical data, recent guidelines developed by NCCN (2006) recommended oral thal/dex as primary therapy (with the caveat that insufficient data exist to recommend treatment duration) as well as salvage therapy for the treatment of MM.

The addition of thal/dex to combination chemotherapy regimens has resulted in response rates as high as 80% in patients with newly diagnosed MM (Schutt et al., 2005; Zervas et al., 2004). However, such regimens are associated with a high rate of thrombotic events—26% with thal/dex added to vincristine plus epirubicin (VED) and 10% with thal/dex added to vincristine plus doxorubicin (T-VAD) (Schutt et al.; Zervas et al.). Ongoing studies will continue to examine the safety and feasibility of adding thalidomide to conventional cytotoxic agents for the treatment of MM.

In the treatment of relapsed, refractory MM, thalidomide typically is initiated at 50–100 mg per day; the average dose in most clinical studies is 200–400 mg per day. Doses greater than 200 mg per day may be associated with increased response rates and longer survival but also with higher toxicity (Ghobrial & Rajkumar, 2003). Doses lower than 200 mg per day may be appropriate for earlier disease stages, in combination with other therapies, or in some subsets of patients. The most common side effects of thalidomide are peripheral neuropathy, constipation, somnolence, and fatigue (Ghobrial & Rajkumar; Zangari, Anaisie, et al., 2001), as seen in Table 1. Peripheral neuropathy affects 50%–80% of patients treated with thalidomide and may limit long-term use of the drug in some patients with MM (Kumar et al., 2003; Tosi et al., 2005). Other side effects are typically, but not always, dose dependent, reversing when thalidomide is discontinued. Higher doses of thalidomide may result in severe skin hypersensitivity (Ghobrial & Rajkumar). Deep venous thrombosis occurs in 1%–3% of patients receiving thalidomide alone and is more frequent when thalidomide is combined with dexamethasone (10%–15%) and/or another cytotoxic agent (10%–26%) (Ghobrial & Rajkumar; Zangari, Anaisie, et al.) (see Table 1). The increased risk of thromboembolic complications can be reduced by therapeutic anticoagulation (Minnema et al., 2004; Zangari et al., 2004). Ongoing studies are investigating the optimal dosing and scheduling of thalidomide in different clinical scenarios.
The need to minimize the nonhematologic toxicity of thalidomide has led to the development of several structural analogs of thalidomide with increased potency and different toxicity profiles (Anderson, 2003). Lenalidomide, a thalidomide derivative with an added amino group at the number four position of the phthaloyl ring, is a member of a new class of novel oral immunomodulatory drugs whose effects include growth arrest or apoptosis of drug-resistant myeloma cell lines, abrogation of myeloma cells’ adhesion to bone marrow stromal cells, and modulation of cytokines that promote the growth, survival, and drug resistance of myeloma cells (Lentzsch et al., 2003; Mitsiades et al., 2002).

Several clinical studies have examined different lenalidomide dosing regimens (see Table 2). In phase I studies in which 46% of patients had received prior therapy with thalidomide, lenalidomide resulted in a 25% or greater reduction in paraprotein in 11 of 24 of patients. Stabledisease (less than 25% reduction in paraprotein) was observed in an additional 8% of patients (Richardson et al., 2002; Zangari, Tricot, et al., 2001). The success of lenalidomide monotherapy in MM has led researchers to further optimize clinical outcomes by using it in combination with other drugs in patients with relapsed, refractory MM (Richardson et

### Table 1. Selected Toxicities of Thalidomide and Their Nursing Management

<table>
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<tr>
<th>SIDE EFFECT</th>
<th>PREVALENCE</th>
<th>INTERVENTIONS</th>
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| Potential teratogenicity | — | • Explain System for Thalidomide Education and Prescribing Safety (S.T.E.P.S.®, Celgene Corporation, Summit, NJ) to patients and caregivers.  
• Monitor beta human chorionic gonadotropin hormone in women of childbearing age once a week for the first month and then every month thereafter for the duration of therapy.  
• Reinforce patient education regarding the use of two methods of birth control. |
| Somnolence and fatigue | Mild: 75%  
Severe: 5%–10% | • Educate patients to take medications in the evening.  
• Review concomitant medications for potential sedative effects. |
| Constipation | Mild: 80%–90%  
Severe: 5% | • Determine patients’ usual bowel habits.  
• Examine patients for abdominal distention.  
• Assess bowel sounds.  
• Bowel regimen  
— Encourage regular exercise according to patients’ abilities.  
— Increase fluid and fiber intake (e.g., prunes, prune juice).  
— Use stool softener or senna-based laxatives (morning and night).  
— Use bowel stimulant, if needed.  
— If no stool occurs in three days, try magnesium citrate, but no more than once a week.  
— Use a laxative as a last resort. |
| Peripheral neuropathy | Mild: 85%  
Severe: 3%–5% | • Assess patients for signs and symptoms of tingling in the distal extremities (fingers and toes).  
• Teach patients to protect extremities from extremes in temperatures.  
• Assess gait.  
• B vitamin and amino acid supplements  
• Dose reduction if necessary  
• Nerve conduction studies may be indicated.  
• Prescription medication if recommended |
| Venous thromboembolism | Thalidomide alone: 4%  
Thalidomide plus dexamethasone and/or another cytotoxic agent: as much as 15% | • Assess patients for signs of swelling or inflammation in lower extremities.  
• Assess patients for complaints of cramping or pain in legs.  
• Assess for Homans’ sign (calf pain at dorsiflexion of the foot)—an indication of deep vein thrombosis.  
• Listen to breath sounds.  
• Be alert to complaints of chest pain.  
• Teach patients the signs and symptoms of thrombus formation and emphasize rapid reporting of symptoms.  
• Encourage exercise.  
• Monitor anticoagulation therapy. |
| Skin rash | Mild: 45% | • Observe skin integrity.  
• Identify type, location, and distribution of rash.  
• Review concomitant medications. Possibly discontinue thalidomide until the cause of the rash is identified.  
• Refer to a dermatologist for accurate diagnosis.  
• Start antihistamines or low-dose steroids as necessary. |
| Neutropenia and anemia | 15%–25% | • Monitor blood counts.  
• Transfusions and growth factors at physician’s discretion |

In a study that evaluated lenalidomide alone and in combination with dexamethasone in patients with relapsed and refractory MM, the overall response rate to lenalidomide monotherapy was 38% (Richardson et al., 2003). Among the patients who received dexamethasone in addition to lenalidomide, 25% experienced a 50% or greater reduction in paraprotein and 33% achieved at least a partial response. Interim analysis of two phase III trials (North-American MM-009 and International MM-010) comparing lenalidomide plus dexamethasone to dexamethasone alone in relapsed and refractory MM showed the combination to significantly increase response rate (61% versus 23% in MM-009) and time to progression (15 months versus 5 months in MM-009) (Celgene Corporation, 2005). In a phase II trial evaluating the safety and efficacy of lenalidomide plus dexamethasone as initial therapy for newly diagnosed MM, 31 of 34 (91%) patients achieved an objective response (Rajkumar et al., 2005).

In the treatment of relapsed, refractory MM, lenalidomide typically is initiated at 25 mg per day. Lenalidomide has different side effects than thalidomide. The most common side effect observed with lenalidomide is predictable and noncumulative myelosuppression that is reversible with dose reduction (Richardson et al., 2002; Zangari, Tricot, et al., 2001). Unlike thalidomide, lenalidomide exhibits virtually no sedative or constipating effects and only rarely neurotoxic side effects (see Table 2). Other side effects of lenalidomide include diarrhea and cramping, which can be managed with diet control and/or dose reduction. Rates of thromboembolic events with lenalidomide monotherapy at doses of 25 mg or less were 2%–3% when reported in phase I and II trials (higher rates were seen with doses of 50 mg in one phase I study [Zangari, Tricot, et al.]). No studies have directly compared the rates of thromboembolic events in patients treated with lenalidomide alone versus in combination with dexamethasone, but unpublished data from the phase III

<table>
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<tr>
<th>STUDY</th>
<th>TREATMENT REGIMEN</th>
<th>EVALUABLE PATIENTS</th>
<th>≥ 50% DECREASE IN PARAPROTEIN (%)</th>
<th>COMPLETE RESPONSE (%)</th>
<th>MAJOR GRADE 3 OR 4 TOXICITIES (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relapsed and refractory multiple myeloma</td>
<td>Lenalidomide (25 mg per day, days 1–21) and dexamethasone (40 mg per day, days 1–4, 9–12, 17–20)</td>
<td>170</td>
<td>35</td>
<td>27</td>
<td>Neutropenia (30), thrombocytopenia (11), anemia (11), thromboembolism (14), and fatigue (6)</td>
</tr>
<tr>
<td></td>
<td>Placebo (days 1–28) and dexamethasone (40 mg per day, days 1–4, 9–12, 17–20)</td>
<td>171</td>
<td>19</td>
<td>4</td>
<td>Thrombocytopenia (6)</td>
</tr>
<tr>
<td>Preliminary phase III data (MM-010 trial) (Celgene Corporation, 2005)</td>
<td>Lenalidomide (25 mg per day, days 1–21) and dexamethasone (40 mg per day, days 1–4, 9–12, 17–20)</td>
<td>176</td>
<td>44</td>
<td>14</td>
<td>Neutropenia (18), thrombocytopenia (10), thromboembolism (8), and fatigue (7)</td>
</tr>
<tr>
<td></td>
<td>Placebo (days 1–28) and dexamethasone (40 mg per day, days 1–4, 9–12, 17–20)</td>
<td>175</td>
<td>18</td>
<td>4</td>
<td>Thrombocytopenia (6)</td>
</tr>
<tr>
<td>Phase II (Richardson et al., 2003)</td>
<td>Lenalidomide (15 mg twice a day versus 30 mg per day, days 1–21)</td>
<td>83</td>
<td>18</td>
<td>6</td>
<td>Thrombocytopenia (18) and neutropenia (28)</td>
</tr>
<tr>
<td></td>
<td>Dexamethasone (40 mg per day, days 1–4 every two weeks) added for progressive disease</td>
<td>30/83</td>
<td>33</td>
<td>NR</td>
<td>–</td>
</tr>
<tr>
<td>Phase I (Richardson et al., 2002)</td>
<td>Lenalidomide (5, 10, 25, 50 mg per day)</td>
<td>24</td>
<td>71</td>
<td>NR</td>
<td>Neutropenia (76) and thrombocytopenia (20)</td>
</tr>
<tr>
<td>Phase I (Zangari, Tricot, et al., 2001)</td>
<td>Lenalidomide (5, 10, 25, 50 mg per day)</td>
<td>15</td>
<td>20</td>
<td>NR</td>
<td>Thromboembolism (33%) and thrombocytopenia (80)</td>
</tr>
<tr>
<td>Newly diagnosed multiple myeloma</td>
<td>Lenalidomide (25 mg per day, days 1–21) and dexamethasone (40 mg per day, days 1–4, 9–12, 17–20)</td>
<td>34</td>
<td>91</td>
<td>6</td>
<td>Fatigue (15), anxiety (6), muscle weakness (6), rash (6), and pneumonitis (6)</td>
</tr>
</tbody>
</table>

* Immunofixation negative
* Greater than 5%
* 25% decrease in paraprotein (%)
* At a dose of 50 mg
NR—not reported
MM-009 trial showed the rates of thromboembolic events to be 10%–15% when lenalidomide was used in combination with dexamethasone and 3%–5% with dexamethasone alone (Celgene Corporation, 2005). The use of prophylactic anticoagulation with the combination of lenalidomide and dexamethasone needs clarification.

Other Novel Oral Agents for Multiple Myeloma

In addition to thalidomide and lenalidomide, several other orally administered drugs that target different pathways involved in the growth and survival of MM cells are being investigated actively and are in early stages of clinical development. They include the farnesyl-transferase inhibitors SCH-66336 and R115777, the VEGF inhibitor PTK787/ZK222584, the histone deacetylase inhibitors suberoylanilide hydroxamic acid and NVP-LAQ824, and the p38 mitogen-activated protein kinase inhibitor (MAPK) SCIO 469 (Hideshima & Anderson, 2002). Trials involving the p38 MAPK inhibitor SCIO 469 are ongoing (Scios, Inc., 2005, 2006).

Role of Oral Agents in Multiple Myeloma and Nursing Implications for Patient Management

The goal of MM therapy is to improve survival and extend duration of response while minimizing toxicity. Selecting the optimal therapy for patients depends on a number of factors, most importantly the toxicity profiles of the agents and individual patient characteristics and comorbidities. Important patient considerations include patients’ ability to comply with the requirements of oral, self-administered agents and patients’ preferences. Given the choice, most patients with cancer prefer oral therapy, citing greater convenience, fewer visits to hospitals and doctors’ offices, and less pain (Liu, Franssen, Fitch, & Warner, 1997). Oral agents such as thalidomide and dexamethasone offer an alternative to current cumbersome chemotherapy regimens and may improve patient quality of life (NCCN, 2006). Novel oral therapies, such as lenalidomide, which are more potent than thalidomide and possess different toxicity profiles, may offer further improvement as lenalidomide, which are more potent than thalidomide and possess different toxicity profiles, may offer further improvement.

Post-treatment schedules, anticipating the appearance of symptoms and further between than for patients receiving IV treatment. Through education and careful monitoring, oncology nurses are instrumental in ensuring that patients with MM are safe and comfortable during the course of oral therapy.

Conclusions

Recent advances in the understanding of the pathogenesis of MM have led to the development of several novel biologic agents that specifically target MM cell growth and survival. Among the agents, oral therapies such as thalidomide and lenalidomide have demonstrated promising activity as monotherapy and in combination with dexamethasone for relapsed and refractory newly diagnosed MM. Thus, oral agents represent a new treatment paradigm for MM and provide alternatives to IV agents at various stages of the disease and its treatment.

Oncology nurses have a vital role in the management of patients with MM, guiding them through the maze of emerging treatment options. Identifying and managing treatment-related symptoms, assessing patients who may be good candidates for self-administered oral therapy, and coordinating primary and supportive care are just a few of the critical roles that nursing professionals must assume as they care for patients with MM.

Clinical trials will continue to define the role of oral agents in the early and advanced stages of MM, with the goal of improving patient outcomes. By researching novel treatment options and partnering with patients in the treatment of their disease, nurses can have a significant positive impact on the future delivery of optimized care.

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