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FEATURE ARTICLE

Understanding Novel Therapeutic Agents for Multiple Myeloma

Joseph D. Tariman, RN, APN, MN, APRN, BC, OCN®

Multiple myeloma (MM) is a B cell malignancy of the plasma cells. It is the second most common hematologic malignancy; only non-Hodgkin's lymphoma is more common. About 14,600 cases of MM will be diagnosed in 2003, and approximately 10,900 people will die of the disease (Jemal et al., 2003). Recently published data on cancer incidence and mortality indicate a consistent decline in mortality rates for most cancers from 1991–1995. However, MM is one of three cancers that showed increased mortality rates for men and women, with increases of 5.6% and 3.6%, respectively (McKean-Cowdin, Feigelson, Ross, Pike, & Henderson, 2000).

People affected by MM often are elderly, with a median age at diagnosis of 65 years. Eighty percent of patients are older than 60 years, and less than 3% are younger than 40 years. African Americans are affected by the disease twice as often as Caucasian Americans. MM is one of the leading causes of cancer death among African Americans (Blade, Kyle, & Greipp, 1996).

MM results from clonal proliferation of plasma cells, which produce a homogeneous immunoglobulin fraction detectable in the serum or urine, called myeloma protein or M-spike. Bone destruction caused by the production of osteoclastic factors by malignant plasma cells is the most characteristic feature of MM, and bone pain is the predominant presenting symptom. Other presenting symptoms include anemia, uremia, recurrent infections, and, less commonly, hypercalcemia, hyperviscosity, polyneuropathy, and spinal cord compression (Lokhorst, 2002).

Multiple myeloma, a B cell malignancy of the plasma cells, remains incurable. Advances in high-dose chemotherapy and stem cell transplantation have improved overall survival and event-free disease periods, but relapses are inevitable. New therapeutic agents have shown promising clinical use in patients with relapsed or refractory multiple myeloma. This article discusses the therapeutic applications of these novel agents with a focus on immunomodulatory drugs, proteasome inhibitors, and arsenic compounds.

Key Words: multiple myeloma, stem cell transplantation, antineoplastic protocols

An oral regimen of melphalan and prednisone was the most frequently used treatment for newly diagnosed MM from 1970–2000. The mean survival rate with this regimen is about 72 months (Trippoli, Messori, Becagli, Alterini, & Tendi, 1998). Clinical trials have tested numerous regimens to improve mean survival from time of diagnosis, but, until recently, none was found to be superior to melphalan and prednisone (Hjorth et al., 1999; Myeloma Trialists' Collaborative Group, 1998).

Recent articles have reviewed the main therapeutic regimens for managing patients with MM (Campbell, 2002; Rajkumar, Gertz, Kyle, & Greipp, 2002; Weber, 2002). The efficacy and safety of high-dose chemotherapy (HDC) and autologous stem cell transplantation is well established in myeloma and considered standard therapy (Goldschmidt et al., 1997; Singhal, 2002). HDC has been used for more than 10 years as treatment for MM, either alone or with autologous hematopoietic stem cell rescue. It has improved remission, event-free survival, and overall survival rates in patients with MM (Attal & Harousseau, 1997; Harousseau & Attal, 1997).

At least one-third of patients with MM do not respond to induction chemotherapy, and those who initially achieve remission (even with HDC) eventually relapse and require additional treatment (Kyle, 1999). Because MM remains incurable and relapse is inevitable, a great need exists for novel therapeutic agents that can prolong life and improve overall survival rates for patients with MM.

Immunomodulatory Drugs

Thalidomide (Thalomid®, Celgene Corporation, Warren, NJ), used empirically to treat MM based on its antiangiogenic activity and the increased angiogenesis observed in MM bone marrow, achieves responses even in refractory, relapsed disease (Singhal et al., 1999). However, thalidomide has significant and dose-limiting side effects (Tariman, 2003), including somnolence, constipation, and neuropathy, which have prompted the search for more potent and less toxic thalidomide derivatives (Richardson, Schlossman, et al., 2002).

Preclinical Studies

Immunomodulatory Drugs (IMiDs™) are potent thalidomide derivatives or analogs that markedly stimulate T cell proliferation, as well

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as interleukin (IL)-2 and interferon-gamma (IFN- γ) production (Corral et al., 1999). CC-5013, also known as IMiD-1 (Revimid[®], Celgene Corporation), a lead IMiD, is 50–2,000 times more potent than thalidomide in stimulating T cell proliferation triggered via the T cell receptor and 50–100 times more potent than thalidomide in augmenting IL-2 and IFN- γ (Richardson, Schlossman, et al., 2002). In addition, CC-5013 triggers dose-dependent decreased secretion of tumor necrosis factor- α (TNF- α), IL-1 β , and IL-6 and triggers increased secretion of IL-10. It also decreases MM cell proliferation by decreasing binding of MM cells to bone marrow stromal cells (BMSCs); inhibits the production in the bone marrow milieu of cytokines (IL-6, vascular endothelial growth factor [VEGF], TNF- α), which mediates the growth and survival of MM cells; blocks angiogenesis; and stimulates host anti-MM natural killer-cell immunity (Davies et al., 2001; Gupta et al., 2001; Hideshima et al., 2000; Richardson, Schlossman, et al., 2002) (see Figure 1).

MM cells secrete a number of cytokines that act on BMSCs, which, in turn, secrete factors that contribute to the growth and proliferation of MM cells. Abnormal IL-1 β expression is believed to stimulate that transition from a clinical condition known as monoclonal gammopathy of undetermined significance to frank MM. IL-1 β is a key activator of osteoclasts, increases the expression of adhesion molecules, and induces the production of IL-6, which is the central regulatory cytokine in the pathogenesis of MM (Hussein, 2002). VEGF, on the other hand, plays a pivotal role not only in neoangiogenesis in MM bone marrow but also in proliferation and migration of tumor cells (Hideshima, Chauhan, Podar, et al., 2001). In preclinical studies, CC-5013 has been found to have strong activity in these multiple pathways of myeloma pathogenesis (Hideshima et al., 2000; Richardson, Schlossman, et al., 2002).

Clinical Studies

Researchers conducting a phase I study of CC-5013 found that it overcame drug resistance and was well tolerated in patients with

relapsed MM. More importantly, no significant somnolence, constipation, or neuropathy occurred among four cohorts of patients who received the drug at different doses of 5, 10, 25, or 50 mg per day. The best responses in myeloma proteins (also called paraproteins) were reductions of greater than or equal to 25% in 12 of 19 evaluable patients (63%) and less than 25% in an additional 3 patients (16%). Study findings supported the antitumor activity and acceptable toxicity of CC-5013 and provided the framework for subsequent studies. Dose-limiting toxicities, including grade three and four leukopenia, neutropenia, and thrombocytopenia, were found in all groups except the 5 mg per day cohort of patients (Richardson et al., 2001).

In a similar phase I study of 15 patients (all patients had chemorefractory disease, having relapsed after at least one HDC treatment with a median of 10 prior cycles of chemotherapy), a more than 50% paraprotein reduction with a

concomitant marrow response occurred in three patients (20%). However, in contrast to the study findings of Richardson et al. (2001), responses were observed only at the 25 and 50 mg dose levels. Significant myelosuppression was observed, even in patients with adequate platelet counts and marrow cellularity. Furthermore, this particular study suggested that CC-5013 has the potential to cause cardiovascular problems such as thromboembolism (two patients) and syncope (one patient) (Zangari et al., 2001).

Promising results from these phase I studies led to a multicenter phase II trial; its findings were presented at the American Society of Hematology conference in December 2002. The trial enrolled 34 patients in three months, with a target accrual of 60 evaluable patients. Preliminary findings of the study were presented. Two cohorts of patients participated; the first cohort received CC-5013 15 mg twice a day and the second cohort received 30 mg once a day for three weeks, followed by a one-week rest period. Nineteen patients were evaluable for paraprotein response with a median follow-up of one month. Best paraprotein reductions across both dose schedules were as follows: 75%–99% in 2 patients (11%), greater than or equal to 50%–75% reduction in 2 patients (11%), greater than or equal to 25%–49% reduction in 2 patients (11%), stable disease (less than a 25% reduction) in 10 patients (52%), and progression (25% increase in paraprotein) in 3 patients (15%). Grade three thrombocytopenia and neutropenia were observed in 4 patients (13%), prompting dose reduction and cytokine support. Somnolence, constipation, neuropathy, or other toxicities were not reported. This study suggests that CC-5013 has an acceptable toxicity profile and the convenience of daily oral dosing (Richardson, Jagannath, et al., 2002).

Ongoing Clinical Trials

With the completion of phase I and phase II trials, CC-5013 currently is being studied in phase III trials in more than 50 U.S. and international clinical trial sites. This final phase aims to enroll 302 patients with relapsed or refractory MM. Its primary objective is comparing the efficacy of oral CC-5013 in combination with oral high-dose pulse dexamethasone to

FIGURE 1. MECHANISMS OF ACTION OF CC-5013 TARGETING MULTIPLE MYELOMA CELLS AND BONE MARROW MICROENVIRONMENT

Note. From "Immunomodulatory Drug CC-5013 Overcomes Drug Resistance and Is Well Tolerated in Patients With Relapsed Multiple Myeloma," by P.G. Richardson, R.L. Schlossman, E. Weller, T. Hideshima, C.S. Mitsiades, F. Davies, et al., 2002, *Blood*, 100, p. 3064. Copyright 2002 by American Society of Hematology. Reprinted with permission.

with oral high-dose pulse dexamethasone to that of placebo and oral high-dose pulse dexamethasone (Weber, 2003).

CC-5013 has the potential to cause myelosuppression; therefore, weekly complete blood count with differential is suggested while patients are on therapy. Dose modifications may be needed based on the degree of myelotoxicity. New Drug Application (NDA) filing for CC-5013 to the U.S. Food and Drug Administration (FDA) is expected after completion of the phase III study.

Bortezomib

Proteasome inhibitor bortezomib, formerly known as PS-341 (Velcade™, Millenium Pharmaceuticals, Inc., Cambridge, MA) is a novel, first-in-class agent that inhibits the 26S proteasome (simply called “the proteasome”). The proteasome is a multicatalytic enzyme present in the nucleus and cytoplasm of all eukaryotic cells (cells with nuclei and other internal organelles). It is a ubiquitous and essential intracellular enzyme that degrades many proteins that regulate cell cycle, apoptosis, transcription, cell adhesion, angiogenesis, and antigen presentation (Adams, 2002a). It consists of the 20S proteasome (the proteolytic core), which is capped on each end by a 19S regulatory complex. The 19S regulatory complexes recognize ubiquitinated proteins and help funnel the protein into the proteolytic core. The proteasome plays a critical role in the coordinated degradation of proteins (or their inhibitors), which regulates cell cycle and cell survival. By degrading regulatory proteins or their inhibitors, the proteasome serves as a central conduit for many cellular regulatory signals and, thus, is a novel target for therapeutic drugs. Proteolysis by the 26S proteasome is a fundamental metabolic process, and complete blockage of the proteasome activity with an inhibitor such as bortezomib results in death for cells and organisms (Adams, 2002a) (see Figure 2).

Preclinical Studies

Bortezomib was tested against a broad range of human tumor cells, including prostate cancer cell lines, and demonstrated that it is able to inhibit intracellular proteasome activity and reduce tumor growth in murine tumor models (Adams et al., 1999). In MM cell lines, bortezomib demonstrated the following activities: It directly inhibited proliferation and induced apoptosis of human MM cell lines and freshly isolated patient MM cells, inhibited mitogen-activated protein kinase growth signaling in MM cells, induced apoptosis despite induction of some mutant

MM cells, overcame drug resistance, added to the anti-MM activity of dexamethasone, and overcame the resistance to apoptosis in MM cells conferred by IL-6 (Hideshima, Richardson, et al., 2001). It also inhibited the paracrine growth of human MM cells by decreasing their adherence to BMSCs and related nuclear factor κ B-dependent induction of IL-6 secretion in BMSCs, as well as inhibiting proliferation and growth signaling of residual adherent MM cells (Hideshima et al., 2002; Hideshima, Chauhan, Schlossman, Richardson, & Anderson, 2001; Hideshima, Richardson, et al., 2001; Mitsiades et al., 2002) (see Figure 3). Leblanc et al. (2002) also recently reported that bortezomib inhibits growth, induces apoptosis, and overcomes drug resistance in human myeloma cells in vitro, supporting the clinical potential of bortezomib to improve patient outcomes.

Bortezomib also has been tested in phase I trials in a variety of tumor types. In these early clinical trials, bortezomib was well tolerated, and preliminary evidence of biologic activity was observed in some patients. Phase II trials in several hematologic malignancies and solid tumor types are in progress (Adams, 2002b).

Clinical Studies

In a phase I study of bortezomib conducted by Orłowski et al. (2002), 27 patients received bortezomib twice weekly for four weeks at either 0.40, 1.04, 1.20, or 1.38 mg/

m², followed by a two-week rest period. Among nine fully assessable patients with heavily pretreated plasma cell dyscrasias completing one cycle of therapy, the researchers found one complete response (CR) and a reduction in myeloma protein levels or decreased marrow plasmacytosis in eight others. In addition, one patient with mantle cell lymphoma and another with follicular lymphoma had shrinkage of nodal disease. Pharmacodynamic studies (direct measurement of whole blood 20S proteasome activity) revealed that bortezomib induced 20S proteasome inhibition in a time-dependent manner, and this inhibition also was related to both the dose in mg/m² and the absolute dose of bortezomib. Dose-limiting toxicities attributed to bortezomib above the 1.04 mg/m² maximum tolerated dose include thrombocytopenia, hyponatremia, hypokalemia, fatigue, and malaise. Researchers concluded that bortezomib was well tolerated at 1.04 mg/m² but patients must be monitored for electrolyte abnormalities and late toxicities. The study also showed that careful assessment and monitoring of patients during therapy are critical, particularly because of bortezomib's potential myelosuppressive adverse effects. Very importantly, the study showed that bortezomib has a promising activity against refractory MM and possibly non-Hodgkin's lymphoma (Orłowski et al.). A phase II study in patients with MM was initiated immediately; results were published recently (Richardson, Barlogie, et al., 2002).

Prior to degradation, doomed proteins first are marked on specific lysine residues with a polyubiquitin chain. Marking the protein is a three-step process in which ubiquitin is activated by a ubiquitin-activating enzyme (E_1), then transferred to a ubiquitin-conjugating enzyme (E_2). E_3 s (the ubiquitin-protein ligases) recognize degradation motifs on specific substrates and catalyze the transfer of ubiquitin from the E_2 to the target. These polyubiquitinated substrates then are recognized and degraded by the 26S proteasome.

FIGURE 2. UBIQUITIN-PROTEASOME PROTEIN DEGRADATION

Note. From “Development of the Proteasome Inhibitor PS-341,” by J. Adams, 2002, *Oncologist*, 7, p. 10. Copyright 2002 by AlphaMed Press. Reprinted with permission.

Bortezomib (formerly called PS-341) targets multiple myeloma in the bone marrow microenvironment.

FIGURE 3. BORTEZOMIB (FORMERLY CALLED PS-341) MECHANISMS OF ACTION

Note. From "Challenging Cases in Myeloma and Plasma Cell Dyscrasias" [Monograph], by K.C. Anderson, 2002, p. 58. Reprinted with permission. Based on information from Hideshima et al., 2002; Hideshima, Chauhan, Schlossman, et al., 2001; Hideshima, Richardson, et al., 2001; Mitsiades et al., 2002.

In the phase II trial, bortezomib demonstrated promising activity in relapsed and refractory MM; clinical benefits included improved hemoglobin level, quality of life, performance status, and levels of non-MM protein immunoglobulins (Richardson, 2002). In this multicenter trial, patients received bortezomib at 1.3 mg/m² by IV push on days 1, 4, 8, and 11 of a 21-day cycle for up to eight cycles. Addition of dexamethasone was permitted in patients with progressive disease after two cycles or stable disease after four cycles. Two cohorts consisted of 202 patients (78 in one group and 124 in the second group). Seventy-eight patients in cohort one had a mean of five prior lines of therapy and a median survival of four years from diagnosis. Of the 202 patients enrolled, 74% previously had received thalidomide and 54% had received HDC. The overall response rate to bortezomib alone was 32% (CR, partial response [PR], and minimal response) in cohort one. Twenty-seven percent had major responses (4% CR, 23% PR), with 9% of the PR patients meeting all of the criteria for CR, with the exception of negative immunofixation; therefore, the CR and near CR rate was 13%. Sixty-eight percent of all of the patients enrolled in the study had either decreased or stable myeloma protein levels (Richardson, Barlogie, et al., 2002). The median duration of response in CR and PR patients had not been reached at 10.2 months (median) follow-up. In this clinical trial, response rate was associated with clinical benefit for patients with relapsed or refractory MM progressing on last therapy (Richardson, Barlogie, et al.).

The adverse effects reported usually were minor and well tolerated by patients (Richardson, 2002). These adverse effects (any grade) included nausea (65%), fatigue (51%), diarrhea (50%), peripheral neuropathy (36%), and thrombocytopenia (36%). Grade three thrombocytopenia occurred mostly in patients with baseline thrombocytopenia, but no serious bleeding was reported. Overall, 80% of patients had baseline neuropathy at study entry, and only four patients without baseline neuropathy developed treatment-emergent neuropathy, with one case of grade three neuropathy (Richardson). Patients should be monitored closely for any of these adverse effects. Failure to assess and lack of appropriate early interventions may jeopardize patients' health conditions. Oncology nurses play a vital role in assessing and monitoring these adverse effects and initiating immediate interventions before serious health conditions or irreversible damage occur.

Ongoing Clinical Trials and Approval by the U.S. Food and Drug Administration

After promising results from phase I and phase II studies, a phase III clinical trial comparing bortezomib with high-dose dexamethasone in patients with relapsed or refractory MM was initiated and currently is accruing patients in more than 50 trial sites across the United States and abroad. The primary purpose of this study is to compare the

efficacy of bortezomib with that of high-dose dexamethasone, a treatment commonly used by clinicians to treat patients with MM (Millennium Pharmaceuticals, Inc., 2002a).

An extension phase II clinical trial also is enrolling patients with the primary objective of determining the time to progression among patients treated with bortezomib 1.3 mg/m². This is an open-label study of bortezomib administered to patients with MM who experienced relapsed or progressive disease after receiving at least four previous treatment regimens or experienced progressive disease after receiving dexamethasone in the phase III study (Millennium Pharmaceuticals, Inc., 2002b).

On May 13, 2003, Millennium Pharmaceuticals, Inc., received approval from the FDA to market Velcade for the treatment of patients with multiple myeloma who have received at least two prior therapies and have demonstrated disease progression on the last therapy (Millennium Pharmaceuticals, Inc., 2003).

Arsenic Trioxide

Arsenic trioxide (Trisenox™, Cell Therapeutics, Inc., Seattle, WA) has been identified and characterized as an effective agent in treating acute promyelocytic leukemia (APL), also known as M3 acute leukemia (Mayorga, Richardson-Hardin, & Dicke, 2002; Niu et al., 1999; Shen et al., 1997; Soignet et al., 1998). Research into the mechanisms by which arsenic targets malignant cell types led to the discovery that arsenic affects myriad pathways that contribute to the cellular transformation process (Novick & Warrell, 2000). This increase in understanding of the mechanisms by which arsenic affects cellular pathways and arsenic trioxide's efficacy in treating APL provided a rationale for investigating the compound's use in treating other hematologic malignancies, such as MM (Anderson, Boise, Louie, & Waxman, 2002; Munshi, 2001). The achievement of clinical responses marked by molecular conversion of the malignant phenotype and remissions in patients who had failed to respond to multiple courses of conventional chemotherapy provided the impetus to explore its use in MM (Anderson, 2002).

In preclinical and clinical studies, arsenic trioxide has shown promise as an effective therapeutic option for the treatment of MM as a single agent or in combination with other drugs (Grad et al., 2001; Hussein, 2001, 2002; Munshi, 2001; Munshi, Barlogie, Desikan, & Wilson, 1999; Munshi, Desikan, et al., 1999; Munshi et al., 2002; Murgu,

2001). Multiple events involved in the pathogenesis of MM coincide with pathways targeted by arsenic trioxide, and early results have suggested that clinical responses and safety are promising in patients with advanced disease (Anderson, 2002).

Preclinical Experience

Preliminary data have suggested that the apoptotic effects of arsenic trioxide are not specific for APL cells but also can be observed in other cell lines, including those of lymphoid and myeloid origin (Calleja, Konig, Warrell, & Gabilove, 1997), and in blast cells from patients with non-M3 acute myeloid leukemia (Lehman, Bengtzen, Paul, & Paul, 1997). The *in vitro* effects of arsenic trioxide on human myeloma cells recently were reported (Rousset et al., 1999). In clinically appropriate concentrations, arsenic trioxide caused a time- and dose-dependent inhibition of survival and growth of myeloma cell lines via apoptosis. Researchers have proposed that ascorbic acid decreases glutathione levels, which, in turn, potentiates arsenic trioxide-mediated apoptosis (Grad et al., 2001). The ability of arsenic trioxide to induce apoptosis in chemosensitive and chemoresistant myeloma cell lines was demonstrated further in another study (Bahlis, Grad, Pandite, & Boise, 2000). Failure to undergo apoptosis may, in itself, be an underlying pathophysiologic defect in MM, and arsenic trioxide appears to cause apoptosis in myeloma cells via alteration in the balance between pro- and antiapoptotic signals (Pearse et al., 1999).

Another investigation reported on the effects of arsenic trioxide on proliferation and apoptosis in MM cell lines (Hussein, 2001). The combination of arsenic trioxide and noncytotoxic concentrations of melphalan resulted in increased sensitivity of MM cells to cell killing. In addition, arsenic trioxide decreased the secretion of VEGF, consistent with previous reports of arsenic trioxide's antiangiogenic properties (Roboz et al., 2000). Such findings are relevant because MM tumor cells are known to secrete VEGF. These results demonstrate the cytotoxic effects of arsenic trioxide on MM cell lines and suggest potential synergistic effects in combination with melphalan and other chemotherapeutic agents. Other investigations have found preclinical synergy with additional agents, including dexamethasone, against MM cell lines (Hayashi et al., 2001).

Clinical Studies

Arsenic trioxide was evaluated in a phase II trial of patients with advanced refractory MM (Munshi et al., 2002). Fourteen patients

with relapsed or resistant MM who received at least one prior cycle of HDC with autologous stem cell rescue were eligible for enrollment. Patients received arsenic trioxide 0.15 mg/kg per day via IV over two hours for as long as 60 days. Patients then were evaluated for response, defined as a reduction in myeloma protein, at least on days 30 and 60. Treatment was continued for an additional 30 days in patients who responded. In this high-risk patient population with extensive prior therapy, 3 of the 14 patients experienced objective response, with myeloma protein reductions of 75% ($n = 1$), 50%–75% ($n = 1$), or 25%–50% ($n = 1$). Objective response occurred in 8 patients, and 3 had progressive disease. Although treatment was reasonably well tolerated in this high-risk population, 11 developed neutropenia, 5 with infectious complications, and 3 developed deep vein thrombosis.

Final results from a phase II study evaluating the use of a higher, less-frequent dose of arsenic trioxide recently were published (Hussein, Mason, Saleh, Rifkin, & Ravandi, 2002). The primary efficacy endpoint was response rate, based on Southwest Oncology Group response criteria, in patients who had relapsed or were refractory to conventional treatment for MM. Arsenic trioxide was administered at a dose of 0.25 mg/kg via IV over two to four hours five days per week during the first two weeks, followed by no therapy for the next two weeks of each four-week cycle. Patients could receive as many as six treatment cycles. Twenty relapsed, and four refractory patients were treated. Three patients were not evaluable for response because of progressive disease or withdrawal of consent during cycle one. Nine of 21 (43%) evaluable patients had objective response as measured by a less than 25% decrease in serum myeloma protein, and eight patients had stable disease. One refractory patient had a 50% decrease in plasmacytoma size. Five patients had arsenic trioxide-related serious adverse effects, which include leukopenia/anemia, anemia/thrombocytopenia, febrile neutropenia, fatigue, and pulmonary edema. Transient increases in transaminase levels occurred in 15 patients during cycle one: (National Cancer Institute Clinical Trials Center) grade one in seven patients, grade two in seven patients, and grade three in one patient) and in four patients during the second and third cycles (grade one and two). No patients were withdrawn, and no doses were decreased because of increased transaminase levels. Fifteen patients had recurrent transient weight gain in most cycles (nine patients had grade one weight gain, five had grade two, and one had grade four). Six of these patients received diuretics. Five patients, including four with preexisting diabetes mellitus, had grade

two hyperglycemia. No patients had alopecia or severe nausea (Hussein et al.).

Preliminary findings of a single-center phase I/II trial of arsenic trioxide in patients with relapsed MM recently were reported (Berenson, Yang, Vescio, Swift, & Sadler, 2002). Patients received arsenic trioxide 0.25 mg/kg twice a week for eight weeks, then no therapy for three weeks in repeated 11-week cycles. Patients who progressed were treated with combination arsenic trioxide and high-dose corticosteroids. The results showed that two of seven evaluable patients had objective response after one cycle of arsenic trioxide, as measured by a less than 25% decrease in serum myeloma protein, and one patient had stable disease. Four patients had progressive disease during or after cycle one. Three patients dropped out before the first scheduled evaluation visit, and one did not meet entry criteria for the study. One drug-related serious adverse effect of epistaxis and anemia occurred. These preliminary results showed that arsenic trioxide is well tolerated at this dose and schedule, both as a single agent and in combination with steroids. The study continues to enroll patients, and the investigator has increased the dose of arsenic trioxide to 0.35 mg/kg using the same schedule. In addition, based on the tolerability of arsenic trioxide and studies that show chemosensitization effects of this drug on myeloma cell lines, further clinical trials are planned using arsenic trioxide in combination with low-dose, oral melphalan (Berenson et al.).

Arsenic trioxide also has been combined with ascorbic acid. In a phase I study of six patients, two had partial response (greater than or equal to a 25% decrease in myeloma protein), and four had stable disease (0%–25% decrease in myeloma protein). No patients experienced dose-limiting toxicities (median two cycles per patient) at 0.15–0.25 mg/kg per day dosing with 500–1,000 mg of ascorbic acid administered via IV within 30 minutes after arsenic trioxide infusion. Grade one or two fatigue was the major side effect reported. Other side effects were sensory neuropathy, nausea, rash, dry skin, leukopenia, and edema. No cardiac arrhythmias were reported. The researchers concluded that arsenic trioxide and ascorbic acid have acceptable toxicity when combined and that promising evidence of activity in refractory or relapsed MM exists (Bahlis et al., 2002). The phase II component of this study is ongoing.

The adverse effects associated with arsenic trioxide administration in patients with MM during clinical trials usually were manageable and well tolerated by patients. In patients with APL, careful monitoring of complete blood count two times per week and chemistries, including potassium and magnesium

levels at least once per week, are essential throughout therapy. These tests are needed to assess for severe myelosuppression and electrolyte imbalances during treatment. Patients also should have a weekly electrocardiogram and be monitored for possible prolongation of the QTC interval and possible atrioventricular block (Cell Therapeutics, Inc., 2002). Close monitoring of patients with MM during therapy with arsenic trioxide also is highly recommended.

Ongoing Clinical Trials

Numerous clinical trials are being sponsored by Cell Therapeutics, Inc., to evaluate the use of arsenic trioxide in patients with re-

lapsed or refractory MM. Several other trials are investigator-sponsored through various academic institutions or oncology collaborative groups (Cell Therapeutics, Inc., Professional Services, 2002) (see Table 1).

Conclusion

CC-5013, bortezomib, and arsenic trioxide have shown clinical activity in patients with MM refractory to conventional therapy. The adverse events or side effects reported in phase II clinical trials usually were reversible and manageable. Healthcare providers should support further investigations of these agents and encourage patients with relapsed or refractory MM to participate in additional

clinical trials of these novel agents. Healthcare providers, particularly nurses, must have adequate knowledge of these new therapeutic agents to ensure safe administration. Potential adverse effects or toxicities are associated with these novel drugs. Careful assessment and monitoring of patients' health status are critical throughout the therapy period. Oncology nurses must keep themselves abreast of the latest information on these novel drugs and develop comprehensive nursing measures that address patients' symptoms.

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TABLE 1. SUMMARY OF ARSENIC TRIOXIDE CLINICAL TRIALS IN MULTIPLE MYELOMA

PROTOCOL TITLE	INVESTIGATOR (INSTITUTION)	TRIAL DESIGN
Combination of arsenic trioxide and ascorbic acid for relapsed or refractory multiple myeloma: A dose- and schedule-finding study based on pharmacokinetics ^a	M. Zangari (Arkansas Cancer Research Center, Little Rock)	Patients will receive arsenic trioxide for five consecutive days, then two days per week for 11 weeks. Ascorbic acid will be given via IV with each dose of arsenic trioxide. Patients with stable disease or response will continue. Cycle = 12 weeks
Phase II study of arsenic trioxide in patients with multiple myeloma (CTI-1057) ^b (closed to accrual)	Multicenter. Primary investigator: M. Hussein (Cleveland Clinic, OH)	Arsenic trioxide is given on days 1–5 and 8–12 (two weeks on and two weeks off). Cycle = four weeks. Evaluation after every second cycle (cycles two, four, and six). Patients may continue on treatment indefinitely without disease progression.
Phase II study of arsenic trioxide in patients with multiple myeloma (CTI-1062) ^c	N. Vey (Institut Paoli-Calmettes, Marseille, France)	Patients will receive arsenic trioxide five days per week for one week followed by twice weekly dosing.
Phase II study of arsenic trioxide twice weekly dosing in patients with multiple myeloma (CTI-1063) ^b	J. Berenson (Cedars-Sinai Medical Center, Los Angeles, CA)	Patients will receive arsenic trioxide twice weekly for eight weeks, then three weeks of no arsenic trioxide. Evaluation every cycle. If patients have progressive disease, they may receive as many as three more cycles at the same dose plus dexamethasone on the day of dosing.
Phase II clinical trial of arsenic trioxide and dexamethasone as therapy for relapsed or refractory multiple myeloma (CTI-1060) ^b	Multicenter. Primary investigator: R. Comenzo (Memorial Sloan-Kettering Cancer Center, New York, NY)	Patients will receive arsenic trioxide daily for five consecutive days, then two days per week. Dexamethasone will be given on days one through five every four weeks. Assessment for myeloma protein is performed every four weeks and bone marrow aspiration every eight weeks.
Phase II study of combination of arsenic trioxide, ascorbic acid, and dexamethasone as therapy for relapsed or refractory multiple myeloma ^a (closed to accrual)	C. Henderson (Access Oncology; Online Collaborative Oncology Group, Memphis, TN)	Patients will receive arsenic trioxide on days one through five, then two times per week for weeks 2–10. Ascorbic acid will be given after every arsenic trioxide infusion. Dexamethasone will be given on days 1–4, 29–32, and 57–60. Cycle = 12 weeks. Evaluation after every second cycle (cycles two, four, and six). Patients may continue on treatment until disease progression or unacceptable toxicity.
Phase I/II trial of arsenic trioxide with ascorbic acid in the treatment of relapsed and refractory multiple myeloma ^a	Primary investigator: K. Lee (University of Miami, FL)	Phase I: dose escalation of arsenic trioxide. Patients will receive ascorbic acid with arsenic trioxide. Phase II: Patients will receive arsenic trioxide Monday through Friday for five weeks; ascorbic acid will be given after every arsenic trioxide infusion. Cycle = seven weeks. Evaluation after every second cycle. Patients may continue on treatment for as many as six cycles without disease progression.
Phase II trial of arsenic trioxide with thalidomide in the treatment of patients with refractory multiple myeloma ^a	J. Hainsworth (Sarah Cannon Cancer Center, Nashville, TN)	Patients will receive arsenic trioxide daily for five consecutive days, then two days per week for three weeks. Patients will receive thalidomide loading dose for the first two weeks, followed by weekly dose escalation of thalidomide.

^a Investigator-sponsored trial

^b CTI trial

^c National Cancer Institute Cooperative Research and Development trial CTI—Cell Therapeutics, Inc.

Note. Based on information from CTI Professional Services, 2002; data on file, CTI Professional Services.

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Rapid Recap

Understanding Novel Therapeutic Agents for Multiple Myeloma

- Multiple myeloma is the second most common hematologic malignancy and most often affects the elderly (the mean age at diagnosis is 65 years).
- Despite advances in high-dose chemotherapy and stem cell transplantation, a third of patients do not respond to induction chemotherapy, and the majority of those who do respond relapse and require additional treatment.
- CC-5013 (an Immunomodulatory Drug™ that is a thalidomide derivative), bortezomib (a proteasome inhibitor), and arsenic trioxide (an arsenic compound) are novel therapeutic agents that have shown clinical therapeutic efficacy against relapsed or refractory multiple myeloma.
- Adverse effects associated with these novel drugs are minor and well tolerated by patients. Careful assessment and monitoring of patients' health status throughout therapy are critical to ensure patients' safety.
- All healthcare providers, especially oncology nurses, should continue to support clinical trials of these novel agents to expedite availability of newer therapeutic options for patients with relapsed or refractory multiple myeloma.