

Arsenic Trioxide: An Emerging Therapy for Multiple Myeloma

NIKHIL C. MUNSHI

University of Arkansas for Medical Science, Little Rock, Arkansas, USA

Key Words. Arsenic trioxide · Multiple myeloma · Antiangiogenesis · Apoptosis

ABSTRACT

Arsenic trioxide can inhibit proliferation and induce apoptosis in multiple myeloma (MM) cells in vitro and in vivo. In addition to affecting tumor growth, arsenic trioxide has been shown to inhibit angiogenesis, suggesting that it may have significant potency in the treatment of MM. Based on these observations, the clinical efficacy of arsenic trioxide was evaluated in patients with advanced refractory MM using a fixed-dose intravenous infusion given daily for a maximum of 60 days. Nine patients were evaluable. All nine had extensive prior therapy; seven had two or more high-dose chemotherapy cycles with autologous stem cell support. All nine patients had cytogenetic abnormalities, and six had chromosome 13 deletions.

Of the four patients who completed more than 30 days of arsenic trioxide infusion, two had >50% reduction in myeloma paraprotein, one had stable disease, and one progressed. Of the five patients with <30 days infusion, two had stable disease and three progressed. Thus, on an intent-to-treat basis, two of nine (23%) patients responded (>50% paraprotein reduction). The regimen was well tolerated except for development of cytopenia, which responded to G-CSF, and a grade III pulmonary complication in one patient. In summary, arsenic trioxide has activity in end-stage, high-risk myeloma and deserves further evaluation in earlier-stage disease. *The Oncologist* 2001;6(suppl 2):17-21

INTRODUCTION

Multiple myeloma (MM) is a B-cell malignancy characterized by an accumulation of monoclonal plasma cells in the bone marrow. The MM clone produces a monoclonal immunoglobulin (M protein) of a specific heavy- and light-chain subtype that may be identified on serum or urine protein electrophoresis and can be used as a surrogate marker of disease activity.

Important characteristics of MM in the U.S. are summarized in Table 1. MM accounts for approximately 1% of all types of malignant disease and about 10% of hematopoietic malignancies (Multiple Myeloma Cancer Resource Center; American Cancer Society webpage, http://www3.cancer.org/cancerinfo/load_cont.asp?ct=30&st=tr). MM accounts for 20% of deaths due to hematologic malignancies. In the U.S., approximately 36,000 individuals are living with MM. The incidence of MM increases with age; the median age at diagnosis is 63 years, and the disease occurs only rarely in patients younger than

40 years [1]. The incidence of MM in African Americans is approximately twice that in whites. Although the incidence of MM has increased in both African American and white individuals within the past 3 decades, this is probably related to improved diagnosis and increased availability and use of medical services [2].

Although definitive causes of MM are unknown, increased risk may be associated with exposure to radiation, herbicides, insecticides, or benzene [1]. MM cells are characterized by a profound genetic instability, and numerous chromosomal translocations and deletions have been identified [3]. Multiple molecular events are probably involved in the pathogenesis of MM, and loss of function of critical genes may contribute to the resistance of MM cells to chemotherapy.

Minimal criteria for a diagnosis of MM is a bone marrow biopsy with results indicating >10% of plasma cells or a plasmacytoma plus a combination of M protein in the serum, M protein in the urine, or lytic bone lesions [1].

Correspondence: Nikhil C. Munshi, M.D., Professor of Medicine, Section of Hematology/Oncology, University of Arkansas for Medical Science, 4301 W. Markham-Slot 776, ACRC Building, Suite 916, Little Rock, Arkansas 72205, USA. Telephone: (501) 686-8250; Fax: (501) 686-6442; e-mail: Munshinikhilc@exchange.uams.edu Received March 23, 2001; accepted for publication March 24, 2001. ©AlphaMed Press 1083-7159/2001/\$5.00/0

Table 1. Multiple myeloma (MM) in the U.S.

1% of all malignancies
10% of hematopoietic malignancies
36,000 individuals living with MM at any one time
13,600 estimated new cases in 2000
11,200 estimated deaths in 2000
63 years, median age at diagnosis

American Cancer Society webpage:
http://www3.cancer.org/cancerinfo/load_cont.asp?ct=30&st=tr.
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With magnetic resonance imaging, bone marrow involvement can appear as diffuse infiltration, focal bone lesions, or a combination of the two patterns.

CURRENT TREATMENT OPTIONS FOR MM

For the past 3 decades, the standard of therapy for MM has been a combination of melphalan and prednisone [4] and response rates have been 40%-60% [5]. However, patients relapse quickly, and the median duration of survival does not exceed 3 years. Attempts have been made to intensify this regimen by using vincristine, doxorubicin, and high-dose dexamethasone or other combinations. However, this has not improved the results of melphalan-prednisone therapy [5, 6].

Within the past decade, high-dose chemotherapy has been identified as an effective treatment option for MM. Earlier, high-dose therapy (140 mg/m² melphalan i.v.) was shown to produce responses, including complete responses, even in patients refractory to conventional chemotherapy. However, this treatment without stem cell support was associated with severe and durable myelosuppression and a high mortality rate [7].

Subsequently, autologous bone marrow transplantation reduced the hematologic toxicity of high-dose melphalan and allowed the use of even higher doses of melphalan and myeloablative regimens with total body irradiation. In numerous studies, high-dose chemotherapy with autologous stem cell support was superior to standard therapy [5, 8]. With this regimen, complete response rates approached 40%, event-free survival was 2-4 years, and overall survival reached 4-6 years.

The first randomized study comparing the two therapies was conducted by the Intergroupe Français du Myelome in newly diagnosed patients under 65 years of age ($n = 200$). Results demonstrated the superiority of high-dose chemotherapy with autologous stem cell support with respect to response rate, event-free survival, and overall survival [5].

A similar advantage for high-dose therapy and autologous stem cell support over conventional chemotherapy was shown in an analysis of 133 patients with advanced MM who were treated with various high-dose regimens [8]. A

long-term analysis from a larger patient population ($n = 1,000$) reported by the same group demonstrated a 5-year continuous complete remission rate of 52% with high-dose therapy in good-risk patients without chromosome 13 abnormalities and with β_2 -microglobulin ≤ 2.5 mg/l, C-reactive protein (CRP) ≤ 4 mg/l, and previous standard chemotherapy of ≤ 12 months duration [9].

One study assessing the timing of high-dose therapy [10] compared patients receiving high-dose therapy upfront with those receiving it as a rescue therapy after failing standard treatment. Overall survival was similar for all patients receiving high-dose therapy, with median survival exceeding 5 years. However, patients who received early high-dose therapy had a shorter duration of treatment and a longer time without symptoms and treatment toxicity than did patients who received late rescue therapy.

Despite improvements in response rates with high-dose therapy and stem cell transplantation, patients continue to relapse. In addition to therapy-related toxicity, the risk of myelodysplastic syndrome is increased in these patients. About 8%-10% of patients ≥ 50 years of age with >12 months of prior therapy develop myelodysplastic syndrome within 7 years of transplantation [11].

PROGNOSTIC FACTORS

Various factors influence survival in MM, including serum β_2 -microglobulin levels, bone marrow plasma cell-labeling index, cytogenic profile, plasmablastic morphology, and other standard clinical laboratory variables [12]. A combination of individual factors appears to provide greater prognostic value. For example, after high-dose chemotherapy, longer survival has been noted in patients without chromosome 13 involvement who have low β_2 -microglobulin and CRP levels and have received < 12 months of prior therapy [9].

Bone marrow microvessel density also has prognostic significance. The bone microenvironment plays a crucial role in regulating growth and survival of MM cells and mediating the resistance of these cells to chemotherapy and radiation [13]. In one study, patients with a bone marrow microvessel density of ≤ 4 per high-power field had superior survival after high-dose therapy [14].

NEW TREATMENT MODALITIES

New treatment modalities are being evaluated to improve response rates achieved with high-dose therapy and to achieve a cure in MM. Areas under investigation include immunotherapy, antiangiogenic agents, and strategies targeted to the bone microenvironment.

Harnessing the graft-versus-myeloma effect observed after allogeneic stem cell transplantation [15] is one of

several immunotherapeutic strategies under investigation. Although allogeneic transplantation after high-dose therapy is associated with response rates higher than those achieved with autologous transplants, treatment-related mortality increases with age and can exceed 50% in older patients (International Bone Marrow Transplant Registry; http://www.ibmtr.org/infoserv/info_sums3.html). Recently, nonmyeloablative allogeneic transplants (minitransplants) followed by donor lymphocyte infusions have reduced transplant-associated toxicity while retaining the beneficial graft-versus-tumor effect of the donor lymphocytes. In addition, various attempts to stimulate the generation of immune responses to MM-specific antigens via vaccination are under way. Methods being evaluated include idiotypic vaccines, fusion of MM cells and dendritic cells to enhance antigen presentation, and DNA vaccines to generate specific humoral and cellular responses against MM antigens. A variety of cytokines, including interferon- α and interleukin 2 (IL-2), have been investigated as adjuncts to therapy.

Antiangiogenic agents are receiving more attention as potential therapies for MM since an association has been made between higher bone marrow microvessel density and poorer outcome [14]. The effects of thalidomide may be mediated at least partially by the agent's antiangiogenic properties. Thalidomide induces marked and durable responses in some patients with advanced, refractory MM, including those who have relapsed after high-dose therapy [16]. Single-agent thalidomide produced an overall 32% response rate. The antimyeloma effect of thalidomide may not be confined to its antiangiogenic properties and may have direct and indirect effects on MM and bone marrow cells that influence cell growth and survival.

A variety of substances produced by endothelial and stromal cells that affect MM cell growth and survival are targets under investigation. Bisphosphonates, a class of agents that indirectly targets stromal cells, inhibit osteoclasts and the production of bone-resorbing cytokines. These agents appear to induce apoptosis, thus demonstrating a direct antimyeloma effect [17].

RATIONALE FOR USE OF ARSENIC TRIOXIDE IN MM

Arsenic trioxide was recently approved for the treatment of acute promyelocytic leukemia (APL). Arsenic trioxide inhibits growth and induces apoptosis in APL cell lines by modulating the localization of the promyelocytic leukemia (PML) and PML-retinal acid receptor- α (PML-RAR- α) fusion proteins [18]. However, its anti-leukemic effects in non-APL myeloid and lymphoid disease appear to occur independently of expression of these proteins. For this reason, arsenic trioxide may be broadly

active against hematologic malignancies other than APL, including MM.

Arsenic trioxide has a variety of in vitro actions on human MM cells and cell lines [19-21]. *Tang et al.* demonstrated that arsenic trioxide induces apoptosis in human MM cell lines via activation of procaspase-3, which triggers cell death by degradation of tumor necrosis factor-receptor inactivating protein [19]. Exogenous IL-6 can prevent apoptosis of MM cells initiated by dexamethasone or serum starvation [22]. However, IL-6 did not protect the cells from arsenic-induced apoptosis. Thus, the mechanism by which arsenic trioxide induces apoptosis in MM cells may be different from that of dexamethasone.

The in vitro studies of arsenic-induced apoptosis in MM cells show that pharmacologic concentrations of arsenic trioxide preferentially trigger MM cell death in nonseparated bone marrow samples from newly diagnosed patients while sparing most myeloid cells [20]. Furthermore, *Park et al.* report inhibition of proliferation of primary MM cells and MM cell lines by arsenic trioxide in a dose-dependent manner [21]. Arsenic trioxide appears to induce cell cycle arrest (G₁ and/or G₂-M phase) by inducing the p21 cyclin-dependent kinase inhibitor protein and by triggering apoptosis through caspase-3 [21]. Finally, arsenic trioxide appears to exert an antileukemic effect in part through inhibition of angiogenesis and thus may have particular potency in the treatment of MM [23].

CLINICAL EXPERIENCE WITH ARSENIC TRIOXIDE IN MM

The first phase II study of arsenic trioxide in MM [24] was designed to assess response to therapy and clinical adverse experiences. Eligible patients had relapsed or resistant MM, at least one prior cycle of high-dose therapy with autologous stem cell rescue, and normal renal and liver function. Patients with a history of grand mal seizure were excluded, as were those with active infection or those who were pregnant or nursing.

Figure 1 summarizes the treatment protocol. Eligible patients ($n = 10$) received a 2-hour daily infusion of arsenic trioxide 0.15 mg/kg for 60 days (the same dosage used in the treatment of APL). Patients were evaluated for response, defined as a reduction in myeloma paraprotein at days 30 and 60. Treatment was continued for an additional 30 days in patients showing a response. Retreatment was initiated in responders between 3 and 6 weeks after first treatment.

Table 2 summarizes the characteristics of the study population. Six of nine evaluable patients had chromosome 13 abnormalities, and all patients had cytogenetic abnormalities.

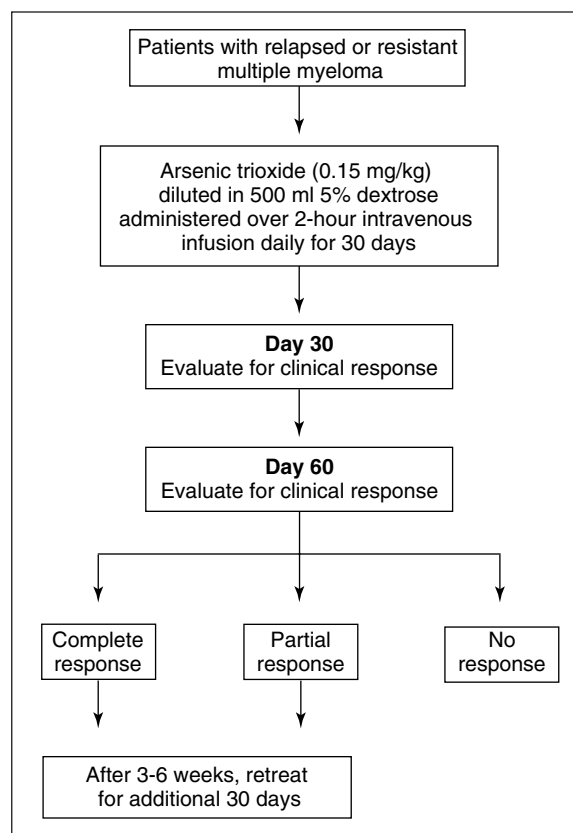


Figure 1. Treatment protocol for patients with relapsed or refractory multiple myeloma. Patients were treated according to the plan outlined.

Patients had advanced disease, relatively high CRP levels, and extensive bone marrow involvement. All patients had received extensive prior therapy. Almost all had received induction therapy, and seven had two or more high-dose chemotherapy cycles with autologous stem cell support. The majority of those relapsing after transplantation had received two salvage therapies (dexamethasone, cyclophosphamide, etoposide, and cisplatin therapy and thalidomide) after relapse.

Of four patients who completed more than 30 days of arsenic trioxide infusion, two had a >50% reduction in serum paraprotein levels, one had stable disease, and one progressed. Of five patients who were treated for <30 days, two had stable disease and three progressed. Thus, two (23%) of the nine

Table 2. Patient characteristics (n = 10)

Parameter	Median	Range
Age (yr)	56	44–71
β_2 -microglobulin (mg/l)	4.4	2.3–6.25
C-reactive protein (mg/l)	26.2	7.2–181
Months of prior therapy	24	12–56

patients showed a clinical response with >50% paraprotein reductions (Table 3).

Of the patients who relapsed or did not respond to treatment, four received salvage treatment; one patient each received a transplantation, high-dose cyclophosphamide/etoposide, dexamethasone and thalidomide, and dexamethasone. However, none of these patients responded to the subsequent treatments, suggesting that they were refractory to multiple therapies.

The toxicities (grades 3-5) reported in MM patients treated with arsenic trioxide were somewhat different from those reported in APL patients. The regimen was well-tolerated except for the development of cytopenia, which responded to G-CSF. Patients were not required to have a normal blood count to enter the study; thus, cytopenia may have been related to previous therapies. One patient developed a grade III pulmonary complication.

CONCLUSIONS

Despite improved response rates achieved with high-dose chemotherapy and stem cell transplantation, MM remains an incurable malignancy. Preclinical data and early clinical evaluation of patients with relapsed or resistant disease support a role for arsenic trioxide in the treatment of MM. Subsequent studies should assess dose escalation and scheduling adjustments for more prolonged administration. Additional basic research may also delineate the mechanisms of action of arsenic trioxide in MM, particularly the effects of arsenic trioxide on angiogenesis. Finally, recent clinical experience demonstrating significant efficacy and acceptable toxicities with arsenic trioxide, even in pediatric patients with APL, provides a strong basis for the use of arsenic trioxide in MM patients with earlier-stage disease.

Table 3. Clinical response to arsenic trioxide therapy

Response (change in paraprotein level)	Infusion <30 days	Infusion >30 days	Both
Reduction 50%-74%	0	2	2
Reduction 25%-49%	1*	0	1
Reduction <24%	2	1	3
Increase >25%	3	1	4
Total	6	4	10

*Continuing treatment

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Oncologist 2001;6;17-21

DOI: 10.1634/theoncologist.6-suppl_2-17

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