Arsenic Trioxide Combined with VCMP or VAD Chemotherapy in Patients with Refractory or Relapsed Multiple Myeloma in a Single Institution of China

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Abstract Arsenic trioxide (ATO) combined with dexamethasone, melphalan or other cytostatic agents had been used to treat refractory or relapsed multiple myeloma (MM) patients. We assessed the safety and efficacy of ATO combined with vindesine/cyclophosphamide/melphalan/prednisone (VCMP) or vindesine/doxorubicin/dexamethasone (VAD) chemotherapy for MM patients who failed more than two different prior regimens. All patients received ATO (0.25 mg/kg day) for 10 days/cycle combined with VCMP or VAD in 30-day cycles. Vindesine (1.4 mg/m²) was given intravenously on day 1, cyclophosphamide (400 mg/m² day) was given intravenously on days 2, 4, 6, 8, 10, melphalan (6 mg/day) and prednisone (1 mg/kg day) were given orally day 1 to day 10 for VCMP regimen. VAD regimen consisted of vindesine 1 mg/day and doxorubicin 10 mg/day intravenously drip for 4 days with oral dexamethasone 40 mg/day for days 1–4, 9–12, 17–20. Patients who completed at least one cycle were evaluated for response to treatment. Objective responses occurred in 35 of 63 (56 %) patients, including seven complete, 14 partial and 14 minor responses. Median progression-free survival and overall survival were 6 and 23 months respectively. 12 patients had elevated serum creatinine levels (SCr) at baseline, and 9 of 12 (75 %) showed

decreased SCr levels during treatment. Frequent Grade 3/4 non-hematological adverse events included arrhythmia, hypertension, fatigue and neuropathy. These results indicate that ATO combined with VCMP or VAD was effective and well tolerated as a new therapeutic option for patients with relapsed or refractory MM.

Keywords Arsenic trioxide · Multiple myeloma · Combined chemotherapy

Introduction

Multiple myeloma (MM) is a common hematological malignant disease characterized by the uncontrolled proliferation of monoclonal plasma cells. Despite improvements in the response rates due to the inclusion of novel drugs as well as high-dose chemotherapy with autologous stem cell transplantation, patients eventually relapse and become resistant to available substances. Therefore, new treatment modalities are being evaluated to improve survival in patient refractory to chemotherapy. Recent studies show that arsenic trioxide (ATO), monotherapy or combined with chemotherapy in the treatment of refractory and relapsed MM has a certain effect. The goal of this paper was to assess the efficacy and toxicity of ATO combined with VCMP or VAD chemotherapy.

Methods

Study Design

This was a single-center, open-label study in patients with relapsed or refractory MM. Informed consent was obtained

Arsenic trioxide monotherapy or combined chemotherapy has demonstrated consistent results in the treatment of refractory or relapsed multiple myeloma. In our study, a total of 63 refractory or relapsed multiple myeloma patients were treated with arsenic trioxide combined VAD or VCMP regimen.

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from all patients prior to entry into the study. All refractory or relapsed myeloma patients received ATO (0.25 mg/kg day) intravenously for 10 days/cycle combined with VCMP or VAD in 30-day cycles. Vindesine (1.4 mg/m²) was given intravenously on day 1, cyclophosphamide (400 mg/m² day) was given intravenously on days 2, 4, 6, 8, 10, melphalan (6 mg/day) and prednisone (1 mg/kg day) were given orally day 1 to day 10 for VCMP regimen. VAD regimen consisted of vindesine 1 mg/day and doxorubicin 10 mg/day intravenously drip for 4 days with oral dexamethasone 40 mg/day for days 1–4, 9–12, 17–20. Patients received a maximum of six treatment cycles. Patients who showed disease progression at any time during the study were eligible to withdrawn from the study and have other drugs or clinical trials.

Patients

Patients were enrolled between January 2009 and January 2013. The inclusion criteria was a diagnosis of MM, age ≥ 18 years. At the time of study entry, patients had to have relapsed following a response to their previous anti-MM treatment, and/or were refractory to their most recent anti-MM therapy. Patients had to have failed at least two different anti-MM regimens prior to study entry. Exclusion criteria included: POEMS syndrome, non-secretory myeloma; plasma cell leukemia, active infection (including human immunodeficiency virus and hepatitis B or C), uncontrolled hypertension, diabetes mellitus or other serious medical or psychiatric illness, history of grand mal seizures, and history of allergic reaction to compounds of similar chemical or biological composition to vincristine, cyclophosphamide, melphalan, doxorubicin or ATO. The institutional review board approved the study and all patients provided informed consent.

Response Criteria

Patients were monitored for response every 4 weeks, before day 1 of each cycle, by quantification of serum immunoglobulins, serum protein electrophoresis and immunofixation, collection of a 24-h urine specimen for total protein and bone marrow smear. CR was defined as negative immunofixation test for myeloma protein in serum and in urine on at least two determinations for a minimum of 4 weeks, no increase in the size of lytic bone lesions, and $<5\%$ plasma cells in the marrow. Partial response (PR) was defined as a $\geq 50\%$ reduction in the level of serum M-protein on at least two determinations 4 weeks apart, reduction in 24-h urinary light-chain excretion by either $\geq 90\%$ or to <0.2 g (if present), $\geq 50\%$ reduction in size of soft tissue plasmacytomas and no increase in size or number of lytic bone lesions. Minor response (MR) was

defined as 25–49 % reduction in serum Mprotein, 50–89 % reduction in urine M-protein (if present), 25–49 % reduction in size of plasmacytomas and no increase in size or number of lytic bone lesions. Progressive disease (PD) was defined as $>25\%$ increase in serum M-protein or in 24-h urinary light-chain excretion, increase in size or development of new existing lytic bone lesions or plasmacytomas or development of hypercalcemia.

Statistical Analysis

Patient characteristics were summarized using the mean and standard deviation for numerical valued variables and frequencies with percentages for categorical variables. Differences in the distributions of patient characteristics between the two groups and associations between variables were assessed using the Kruskal–Wallis test for numerical variables or generalized Fisher exact tests, for categorical variables. Unadjusted probabilities of OS and PFS were estimated using the method of Kaplan and Meier. The log-rank test was used to compare unadjusted OS and PFS between subgroups.

Results

Patient Characteristics

From January 2009 to January 2013, 63 patients included three patients who failed autologous transplant were assigned to ATO combined chemotherapy. 20 patients were treated with VAD+ATO regimen and 43 patients received VCMP+ATO regimen. The patients of two groups were well matched clinically. Table 1 summarizes the characteristics of the 63 patients enrolled in this study.

Response and Efficacy of ATO Combined Therapy

The overall response of the patients was 56 %. CR was observed in seven patients (11 %), PR in 14 patients (22 %) and MR in 14 patients (22 %). There was no significant difference between the overall responses of VAD+ATO and VCMP+ATO group (50 vs. 58 %, $P > 0.1$). Median follow-up among living patients was 19 months (range 4–26 months). The median progression-free survival was 6 months (range 0.5–14 months). The overall survival (OS) was 23 months (2–60 months). The time to response and the duration of response, the OS and PFS for different combined therapy were as follows (Table 2; Figs. 1, 2). The OS and PFS of patients with high-risk cytogenetics were 19 months (range 2–26 months) and 4 months (range 0.5–8 months). The OS and PFS of patients in different groups and were significantly different ($P < 0.05$). According to Mayo risk

Table 1 The baseline characteristics of patients ($n = 63$)

	Total	VAD+ATOgroup (n)	VCMP+ATO group (n)
Sex			
Female	28	8	20
Male	35	12	23
Mean age (range) years	58 (35–72)	59	57
Type			
IgG type	28	10	18
IgA type	14	4	10
Light strain	14	4	10
Non-secretory	7	2	5
Stage			
I	7	2	5
II	14	4	10
III	42	14	28
Renal impairment	12	4	8
Refractory	28	9	19
Relapsed	35	12	23
High-risk cytogenetics			
No	29	9	20
Yes	34	12	23
Median number (range) of failed therapies	6 (2–15)	6	6
Number of patients by failed therapies			
VCMP	41	14	37
VAD	32	11	21
Bortezomib	4	1	3
Thalidomide	58	20	38
Peripheral stem cell transplant	1	0	0
Serum M-protein (g/l) mean (range)	28 (0.5–66.4)	26	29
Urine M-protein (g/24 h) mean (range)	1.8 (0.19–4.3)	1.9	1.7
β 2-Microglobulin (mg/dl) mean (range)	5.5 (0.5–8.6)	5.2	5.7

stratification for myeloma, the high risk cytogenetics included deletion of chromosome 13, hypodiploidy and t(4;14), t(14;16) or 17p- by fluorescent in situ hybridization [12]. Over expression of fusion gene caused by translocation of 14q32/IGH gene results in the secretion of M protein and

forms the biological characteristics of the plasma cell tumor, but it often don't affect the prognosis. The prognosis of patients with some triploid (such as +6, +9 and +17) is good, because these cytogenetic abnormal results the compensatory expression of tumor suppressor gene.

Table 2 Patients responses to ATO combined therapy ($n = 63$)

Responses n (%)	VAD+ATO	VCMP+ATO
Overall response	10 (50)	25 (58)
Complete response	2 (10)	5 (12)
PR	5 (25)	9 (21)
Minimal response	3 (15)	11 (26)
Time to response (months) median (range)	2.5 (1–6)	2 (1–5)
Duration of response (months) median (range)	6 (1–10)	8 (1–16)
OS	20 (2–49)	26 (2–60)
Progression-free survival (months) median (range)	5 (0.5–12)	7 (1–14)

Serum Creatinine (SCr) Levels During ATO Combined Therapy

At baseline, 12 of 63 patients (19 %) had SCr levels $\geq 176.8 \mu\text{mol/L}$. During the study, 9 of these 12 patients (75 %) showed a reduction in SCr levels, and 2 (17 %) had SCr levels reduced to normal at some point during the study (Table 3).

Adverse Effects

All patients were evaluable for safety and tolerability. 29 % patients had Grade 3 or 4 adverse events. Frequent

Fig. 1 The OS and PFS of patients with ATO combined therapy. **a** OS, **b** PFS

Fig. 2 The OS and PFS of patients with or without high-risk cytogenetics. **a** OS, **b** PFS

Table 3 Baseline and best SCr levels during ATO combined therapy

Patient no.	Baseline SCr ($\mu\text{mol/L}$)	Best SCr ($\mu\text{mol/L}$)	% Change
1	524.3	467.5	−11
2	512.8	384.3	−25
3	386.5	241.3	−38
4	298.7	205.6	−31
5	196.1	180.2	−8
6	289.4	102.3*	−65
7	179.6	89.7*	−50
8	201.3	188.4	−6
9	462.3	276.2	−40
10	413.5	326.7	−41
11	385.2	296.1	−23
12	326.9	197.8	−39

The significance of asterisk was that the renal function of these patients were normal. The normal range of Scr was 40–120 $\mu\text{mol/L}$

Grade 3/4 included arrhythmia, hypertension, fatigue, and neuropathy. The most frequent 1/2 non-hematological adverse event was nausea and vomiting. Grade 3–4 adverse events were more common in VAD+ATO group than that in VCMP+ATO group (Fig. 3).

Discussion

MM is a B cell malignancy characterized by an accumulation of monoclonal plasma cells and the production of monoclonal immunoglobulin. Traditional chemotherapy and hematopoietic stem cell transplantation could prolong the OS of MM patients, but nearly all MM patients will eventually develop chemoresistance. Traditional chemotherapeutic agents for chemoresistant relapsed and/or refractory MM typically only achieve response rates of 10–30 %,

Fig. 3 Adverse events of ATO combined therapy

generally lasting only several months. Current treatment options of refractory or relapsed MM included immunomodulatory drugs, proteasome inhibitors, histone deacetylase inhibitors, and other targeted agents, but the response rates were limited. ATO has been used as therapeutic agents for thousands of years. It was firstly be used to treat acute promyelocytic leukemia. Recent years, researchers found that ATO can induce the apoptosis of myeloma cells in vitro and vivo. ATO has been shown to increase the intracellular accumulation of doxorubicin in hepatocellular carcinoma [1]. Furthermore, ATO produces polymerization of microtubules and mitotic arrest in human cell lines, indicating a potential role in overcoming resistance to vinca alkaloids. Finally, ATO has overcome steroid resistance in myeloma cell lines by manipulating the cellular redox state. Now, we used ATO to treat relapsed or refractory MM patients. Mohamad et al. reported 24 MM patients (8 had relapsed and 16 were refractory to prior therapy) who received ATO monotherapy. Reductions (25 % or more) in serum M-protein levels occurred in 33 % patients. 25 % patients had stable disease. The median time to response was 67.5 days, with a median duration of response of 130 days [2]. Another Phase II Single-Arm Study shows that ten refractory MM patients received ATO monotherapy, stable disease was observed in four patients (33 %), progression disease in five patients (41.6 %), complete response in one patient (3.8 %) [3]. Overall response rates of using ATO in addition to dexamethasone, melphalan or other cytostatic agents varied widely between 12 and 100 %. Complete remissions were achieved in the minority of cases (range 0–25 %). Most of the OR rates comprised PR and MR. The duration of responses varied greatly between studies, ranging from 0 to 24 months [4–8]. In this study, we found that the overall response of the patients was 56 %. CR was observed in seven patients (11 %), PR in 14 patients (22 %) and MR in 14

patients (22 %). The median progression-free survival was 6 months (range 0.5–14 months). The OS was 23 months (2–60 months). It was consistent with the reported literature.

Mostly, ATO combined with ascorbic acid or dexamethasone or bortezomib or thalidomide were used to treatment refractory or relapsed MM patients. In a Phase II clinical trial of ATO with liposomal doxorubicin, vincristine, and dexamethasone in 11 newly diagnosed MM. There were four partial and no complete responses [9]. We combined VAD+ATO to overcome the drug resistance for relapsed or refractory MM patients. The overall response rate of VAD+ATO was 50 %, and the OS and PFS of patients in the VAD+ATO group were 20 and 5 months respectively. Our hospital improved the MP regimen, and made use of the combination regimen vindesine, cyclophosphamide, melphalan and prednisone (VCMP) for the newly diagnosed myeloma patients. The overall response rate was nearly 60–70 %. Now we combined VCMP+ATO for refractory or relapsed myeloma patients. It was showed that there was no significant difference between the overall responses of VCMP+ATO group and VAD+ATO (58 vs. 50 %, $P > 0.1$), and the OS and PFS of patients in the VCMP+ATO group were 26 and 7 months. Compared with VAD+ATO, VCMP+ATO regimen included melphalan and cyclophosphamide, which would more conducive to overcome drug resistance, and in clinical observation, we found VCMP regimen was modest and had better patient compliance and tolerance, so we inferred the OS and PFS of patients treated with VCMP+ATO regimen were longer than that of VAD+ATO regimen. The results confirmed this point.

The influence of cytogenetics has also been examined in patients with relapsed or refractory MM, with varying results. As an example, bortezomib in combination with doxorubicin and dexamethasone showed comparable activity in relapsed or refractory patients with or without del13q [10]. In contrast, relapsed or refractory MM patients treated with lenalidomide plus dexamethasone exhibited comparable time to progression (TTP) and OS regardless of del13q or t(4;14) status, whereas patients with del17p13 experienced worse time-to-event outcomes. Similarly, the presence of a non-hyperdiploid karyotype, other poor-risk cytogenetic abnormalities [i.e., presence of del13q, del17p, add1q21, t(4;14), or t(14;16)], and thalidomide-refractory disease were associated with reduced responses (less than a PR) to treatment with lenalidomide and dexamethasone alone or in combination with bortezomib [11]. These findings suggest that the presence of high-risk karyotypic abnormalities which included chromosome 13, hypodiploidy, t(4;14), t(14;16) or 17p- may define subsets of patients more likely to benefit from targeted therapies [12]. Furthermore, new agents that improve PFS or OS in high-risk patients are of particular interest in the treatment of relapsed or refractory MM.

In our study, the OS and PFS of patients with high-risk cytogenetics were 19 months (range 2–26 months) and 4 months (range 0.5–8 months). It suggested that VCMP+ATO or VAD+ATO may improve the prognosis of the patients with high risk cytogenetics.

Bortezomib is effective in patients experiencing relapse with creatinine clearance ≤ 50 mL/min [13–16]. Reduced-dose lenalidomide is feasible in patients with MM with renal impairment. Nevertheless, implementation of lenalidomide therapy for patients with relapsed MM with renal impairment is feasible. In this study, 19 % patients had elevated SCr levels at baseline, suggesting some degree of renal insufficiency in these patients. Most of these patients showed a reduction in SCr levels while on ATO combined chemotherapy, suggesting that ATO combined chemotherapy may potentially improve renal function in patients with elevated baseline SCr. Importantly, patients with elevated baseline SCr levels treated with ATO combined chemotherapy not only experienced response rates and tolerability similar to patients with normal baseline SCr levels, but also showed frequent improvement in their SCr levels. These observations warrant further evaluation of the impact of ATO combined chemotherapy on renal function.

The ATO combined chemotherapy was well tolerated and 29 % patients had Grade 3 or 4 adverse events. Frequent Grade 3/4 included arrhythmia, hypertension, fatigue, and neuropathy. The most frequent 1/2 non-haematological adverse event was nausea and vomiting. All the adverse events were improved by symptomatic or supportive treatment.

The results of this study showed that the ATO combined chemotherapy is an effective and well-tolerated treatment for heavily pretreated patients with relapsed or refractory MM.

Conflict of interest All other authors state that they have no conflicts of interest.

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