Multiple Myeloma

Phase II multicenter study of arsenic trioxide, ascorbic acid and dexamethasone in patients with relapsed or refractory multiple myeloma

Arsenic trioxide induces growth inhibition and apoptosis in multiple myeloma cell lines. Reducing glutathione by ascorbic acid may enhance the efficacy of arsenic trioxide. Here we report the results of an international multi-center study of arsenic trioxide in combination with ascorbic acid and dexamethasone as treatment for patients with advanced multiple myeloma.

A total of 20 patients with relapsed and/or refractory multiple myeloma (MM) were included in this phase II study. Their median age was 65 years (range, 41–76 years); 11 patients had IgG, six patients IgA and three patients had light-chain MM. All patients had received one or more lines of treatments with chemotherapy. The median number of prior treatments was four (range, 1-8).

Eleven patients had received high-dose dexamethasone, 17 patients had been treated with thalidomide and nine patients had received high-dose melphalan with autologous stem cell support.

Arsenic trioxide (ATO, Trisenox®), ascorbic acid (AA) and dexamethasone were administered during 3 weeks in a 4-week cycle. In the first cycle, during the first week, a loading-dose of ATO was administered intravenously (IV) over 1-2 hours at a dose of 0.25 mg/kg per day for 5 days. AA 1000 mg was administered IV over 15 minutes within 30 minutes after each ATO infusion and dexamethasone was given at a dose of 40 mg per day orally for 5 days. During the second and third week, the patients received a maintenance dose of twice weekly ATO at 0.25 mg/kg IV, AA 1000 mg IV and dexamethasone 20 mg orally. In the second, third and fourth cycles, the patients received a maintenance dose of twice weekly ATO 0.25 mg/kg IV, AA 1000 mg IV and dexamethasone 20 mg orally. Patients were scheduled to receive a minimum of four treatment cycles. Patients who achieved at least a minimal response within cycles 1-4, continued to receive two additional treatment cycles. Treatment was withheld in the case of grade 4 hematologic or any grade 3-4 non-hematologic toxicity (NCI Common Toxicity Criteria, version 2) considered to be treatment-related. For non-hematologic toxicity, the treatment was withheld until the toxicity returned to grade 2 or less and for hematologic toxicity until the toxicity returned to grade 3 or the hemoglobin, absolute neutrophil count and platelet count returned to baseline values. If the toxicity did not resolve within 1 month, as defined above, the treatment was discontinued. Dose reduction of arsenic trioxide was not allowed. Response evaluation was based on the criteria of the EBMT.1

At the time of analysis, 11 patients (55%) were still alive. The median follow-up from the start of treatment was 9 months (range, 1-20 months). Of the 20 patients, 14 completed two or more cycles of therapy: two cycles (n= 2), three cycles (n=2), four cycles (n=6), five cycles (n=1) and six cycles (n=3). Ten patients (50%) discontinued treatment early before the fourth cycle because of toxicity (n=3) or progressive disease (n=7). A clinical response was observed in eight of 20 patients (40%), including a partial response in two and a minor response in six patients. The median duration of response was 5 months (range, 0->10 months). The median progression-free survival was 4 months and the median overall survival was 11 months (Figure 1).

These results were inferior to those of other studies in which arsenic trioxide was combined with AA and traditional chemotherapeutic agents such as melphalan2 and dexamethasone.2 A possible explanation for the less favorable response may be that our study patients had been more extensively pre-treated.

The exact mechanism of action of ATO is unknown.4 Preclinical studies suggest a possible synergism between ATO, AA and dexamethasone. It is, however, difficult to

Figure 1. Overall survival (OS) and progression-free survival (PFS).

Figure 2. Adverse events according to Common Toxicity Criteria (CTC).
determine the contribution of each individual agent to the response. Of note, four of the eight responders in our study had received prior high-dose dexamethasone. The most common adverse events were bacterial infections (n=10), peripheral edema (n=8), fatigue (n=7), dyspnea (n=6), reactivation of herpes zoster (n=5), neuropathy (n=5), neutropenia (n=4), thrombocytopenia (n=3) and malaise (n=3) (Figure 2). The majority of the adverse events were low grade (CTC grade 1-2). One patient had a venous thromboembolic event. QT-interval prolongation was observed in one patient but did not require any specific intervention. Grade 3-4 adverse events included bacterial infections (n=6), neutropenia (n=3), hepatic toxicity (n=5) and thrombocytopenia (n=2).

Genetic polymorphisms in the arsenic methylation pathway may have a role in the toxicity of this drug. Although the number of observations in this trial was small, we found no difference in toxicity based on the active wild-type or inactive mutant genotype for ABCB1, GSTP1, GSTM1 or GSTT1.

In conclusion, combination therapy with arsenic trioxide, ascorbic acid and dexamethasone is feasible, but has moderate efficacy and significant toxicity in heavily pretreated patients with advanced MM. So far, the results of ATO-based regimens are inferior to those of other new agents such as bortezomib and lenalidomide.

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References