Efficacy and Safety of Melphalan/Arsenic Trioxide/Ascorbic Acid Combination Therapy (MAC) in Patients with Relapsed/Refractory Multiple Myeloma: A Prospective, Multi-Center, Phase II, Single-Arm Study

Abstract

[Abstract text]

Introduction

Despite the promising activity of treatment options for patients with multiple myeloma (MM), the disease is usually incurable. Combination chemotherapy is the standard treatment for patients with relapsed/refractory multiple myeloma. However, most patients develop resistance to the chemotherapeutic agents used and develop refractory disease. In a SCID-hu human myeloma model, arsenic and melphalan have shown clinical activity in MM. Recent studies have shown that ascorbic acid (AA) improves the anti-MM effects of ATO as well as those of melphalan. The MAC regimen has been shown to be effective in MM, but to date no clinical trials have been conducted with patients who have relapsed/refractory disease.

Objectives

- To assess the time to response, progression-free survival, and overall survival
- To assess the safety and tolerability of MAC therapy

Study Design

[Study design table]

Treatment schema (Table 1)

- Patients received melphalan orally at a dose of 0.1 mg/kg daily for the first 4 days of each 6-week cycle. ATO (0.25 mg/kg IV) was administered daily on days 1–4 and 15–16 of each 6-week cycle.
- ATO was administered at 2.15 mg/m² on days 1–4 and 15–16 of each 6-week cycle.

Table 1. Treatment scheme

Cycle
Week
Melphalan (0.1 mg/kg)
Arsenic trioxide (0.25 mg/kg)
Ascorbic acid (200 mg/24 hours)
1–2
1–4 daily
1–4 daily
3–4 daily
3–4 daily
2–5
1–4 daily
1–4 daily
3–4 daily
3–4 daily
Table 2. Patient demographics and baseline characteristics (N = 65)

<table>
<thead>
<tr>
<th>Median age (range), yr</th>
<th>66 (20–89)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median number (range) of failed therapies</td>
<td>6 (1–11)</td>
</tr>
<tr>
<td>Number of patients by failed therapies</td>
<td>25 (PD), 25 (MR), 15 (SD)</td>
</tr>
<tr>
<td>Renal function</td>
<td>2–5</td>
</tr>
<tr>
<td>SCr, mg/dL</td>
<td>2.6</td>
</tr>
<tr>
<td>B UN (mg/dL)</td>
<td>20.0</td>
</tr>
<tr>
<td>B UN (mg/dL)</td>
<td>1.7</td>
</tr>
</tbody>
</table>

Table 3. Patient responses to MAC therapy (N = 65)

- 31 patients (objective response rate = 48%) responded to the MAC treatment regimen.
- 12 (71%) of these 17 patients had at least disease control with the MAC treatment regimen.
- Median progression-free survival was 7 months (Figure 1).

Table 4. Change in renal function during MAC therapy among patients with elevated serum creatinine at baseline (n = 23)

- Median progression-free survival was 7 months (Figure 1).

Results

- A total of 65 patients with relapsed or refractory MM were enrolled (Table 2).
- Clinical responses:
  - 31 patients (objective response rate = 48%) responded to the MAC treatment regimen (Table 3).
  - Median disease duration of response was 11 months.
  - 19 patients with objective responses and 18 patients with stable disease completed 6 cycles of MAC therapy (Table 4).
- Safety:
  - The MAC regimen was well tolerated, with few adverse events reported.
  - No patient developed renal toxicity, and no patient died.
  - The MAC regimen did not induce neuropathy.
  - Patients with pre-existing neuropathy did not experience any worsening of their condition.

Figure 2. Kaplan-Meier estimates of overall survival of patients receiving MAC therapy

Figure 3. Kaplan-Meier estimates of renal function during MAC therapy

Figure 4. Kaplan-Meier estimates of progression-free survival of patients receiving MAC therapy

Conclusions

- MAC therapy is an active regimen in patients who have failed multiple therapeutic options.
- Responses to MAC therapy were observed in 48% of patients in this heavily pretreated group.
- MAC therapy was well tolerated.

References

[List of references]

Table 5. Serious adverse events (N = 65)

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### Study Design

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<tr>
<th>Cycle</th>
<th>Week</th>
<th>Dosage (mg)</th>
<th>Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2-5</td>
<td>100/1.5/1.5</td>
<td>SC</td>
</tr>
<tr>
<td>1</td>
<td>5</td>
<td>20/1.5/1.5</td>
<td>SC</td>
</tr>
</tbody>
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</tr>
<tr>
<td>5</td>
<td>20/1.5/1.5</td>
<td>SC</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Median age (range), yr</th>
<th>Median CR (range), %</th>
<th>CR, complete response; SD, stable disease</th>
</tr>
</thead>
</table>

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<table>
<thead>
<tr>
<th>Objective responses in evaluable patients</th>
<th>N (%)</th>
<th>CR, complete response; SD, stable disease</th>
</tr>
</thead>
</table>

#### Table 4. Change in renal function during MAC therapy among patients with elevated serum creatinine at baseline (N = 23)

<table>
<thead>
<tr>
<th>Patient #</th>
<th>Baseline (g/L)</th>
<th>Best (g/L)</th>
<th>% Change</th>
<th>Best response</th>
</tr>
</thead>
</table>

### Results

**Objective responses** in evaluable patients were as follows:

- **CR**: 35/65 (54%)—17/25 (68%) had complete remission with >90% reduction in serum paraprotein.
- **SD**: 30/65 (46%)

**Table 5. Serious adverse events (N = 65)**

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>N (%)</th>
</tr>
</thead>
</table>

### Conclusions

- **MAC therapy** is now in use in patients who have failed multiple therapeutic regimens.
- **Response** to MAC therapy was associated with improvements in SQI scores in patients with both MM and CR.
- **MAC therapy** was well tolerated.

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**References**


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**Safety**

- **The MAC regimen** was well tolerated, with few adverse events reported.
- **No adverse events** were serious.
- **Fluid retention** responded well to diuretics and/or steroids.
- **The MAC regimen** did not induce neuropathy.
- **Patients** with preexisting neuropathy did not experience any worsening of their condition.
### Study Design

**Treatment scheme (Table 1):**

<table>
<thead>
<tr>
<th>Cycle</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Treatment</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Days</td>
<td>1-4</td>
<td>1-4</td>
<td>1-4</td>
<td>1-4</td>
<td>1-4</td>
<td>1-4</td>
</tr>
<tr>
<td>Route</td>
<td>PO</td>
<td>IV</td>
<td>IV</td>
<td>PO</td>
<td>IV</td>
<td>IV</td>
</tr>
<tr>
<td>Dose</td>
<td>0.1 mg/kg</td>
<td>0.25 mg/kg</td>
<td>0.25 mg/kg</td>
<td>0.1 mg/kg</td>
<td>0.25 mg/kg</td>
<td>0.25 mg/kg</td>
</tr>
<tr>
<td>Agent</td>
<td>Melphalan</td>
<td>ATO</td>
<td>ATO</td>
<td>Melphalan</td>
<td>ATO</td>
<td>ATO</td>
</tr>
</tbody>
</table>

**Patient assessments:**

- **Malignant disease assessment:** Included family history, marital status, and family history of malignancy, medical history, and family history of malignancy. Melphalan-induced cytotoxic effects.1 ATO overcomes chemoresistance by inducing apoptosis through pathways through inhibition of NK-2 mechanisms: (1) mitochondrial membrane depolarization and activation of downstream apoptotic

**Objective responses were observed in 31 (48%) patients, including 2 complete (CR), 15 partial (PR), and 14

**Introduction**

Despite the expanding array of treatment options for patients with multiple myeloma (MM), the

**Objectives**

- **Primary:** To determine the response rate (complete response [CR] + partial response [PR] + minor response [MR])
- **Secondary:** To determine the time to progression of disease

**Conclusions**

- **MM therapy is an active regimen in patients who have failed multiple treatments:**
- **Responses to MAC therapy were associated with improvements in SCr levels in patients with baseline azotemia.**
- **Durable responses as well as improved renal function for the patients with baseline azotemia.**
- **Supporting by Cephalon, Inc., Frazer, Pennsylvania, USA.**