**MULTIPLE MYELOMA**

**ARSENIC TRIOXIDE**
Arsenic trioxide 0.25 mg/kg/day IV  Monday – Friday of Weeks 1 and 2

*Administer over 1 hour; **Administer Monday – Friday (5 days per week) during the first 2 weeks of each 4 week cycle.

Repeat cycles every 28 days.

NOTE: Ensure that serum electrolytes are assessed and corrected, particularly potassium and magnesium, prior to start of treatment, and maintain these values throughout the cycle. Avoid medication known to prolong the QTc interval. Obtain a 12-lead ECG prior to the first dose and ensure that the QTc interval is not greater than 460 msec.


**BORTEZOMIB**
Bortezomib 1.3 mg/m² IVB Days 1, 4, 8 and 11

Repeat cycle every 21 days to a maximum of 8 cycles.

NOTE: Patients with progressive disease after 2 cycles or stable diseases after 4 cycles were able to receive dexamethasone 20 mg on the day of and the day after bortezomib.


**BORTEZOMIB – DOXORUBICIN – DEXAMETHASONE**
Bortezomib 1.3 mg/m² IVB Days 1, 4, 8 and 11
Dexamethasone 40 mg/day PO See below (cycle dependent)
Doxorubicin 9 mg/m²/day IV Days 1 – 4

Repeat cycle every 21 days for 4 cycles.

NOTE: Dexamethasone dosing: 40 mg PO/day was administered on days 1 – 4, 8 – 11, and 15 – 18 of cycle 1 and on days 1 – 4 of cycles 2 – 4. Concurrent bisphosphonate therapy, gastric protection, erythropoietin and *Pneumocystis carinii* prophylaxis were given.

DOSE MODIFICATIONS: Treatment was withheld for up to 2 weeks in the event of grade 3–4 non-hematological toxicity, febrile neutropenia or grade 4 hematological toxicity. Dose reduction of bortezomib by 25% occurred in the event that 2 doses were withheld. Dose reductions of bortezomib from 1.3 to 1 mg/m² proceeded in the event of grade 2 peripheral sensory neuropathy with or without grade 1 painful neuropathy, or grade 2 painful neuropathy alone. A reduction from 1.3mg/m² to 0.7 mg/m² proceeded with grade 3 sensory or grade 2 painful neuropathy with sensory symptoms. Combined grade 3 sensory and painful neuropathy or any grade 4 neuropathic event resulted in discontinuation of bortezomib.

### CYCLOPHOSPHAMIDE – PREDNISONE

Cyclophosphamide  150–250 mg/m²* IV/PO  Weekly
Prednisone  100 mg QOD  PO  Alternate days

*Maximum dose 500 mg.


### DCEP (DEXAMETHASONE – CYCLOPHOSPHAMIDE – ETOPOSIDE – CISPLATIN)

Dexamethasone  40 mg/day  PO  Days 1 – 4
Cyclophosphamide  400 mg/m²/day  CIVI*  Days 1 – 4
Etoposide  40 mg/m²/day  CIVI*  Days 1 – 4
Cisplatin  10 mg/m²/day  CIVI*  Days 1 – 4

Cisplatin, etoposide, and cyclophosphamide can be combined together in 1000 mL NS and infused.


### DTPACE (DEXAMETHASONE – THALIDOMIDE – CISPLATIN – DOXORUBICIN – CYCLOPHOSPHAMIDE – ETOPOSIDE)

Dexamethasone  40 mg/day  PO  Days 1 – 4
Thalidomide  400 mg/day  PO**  Daily
Cisplatin  10 mg/m²/day  CIVI*  Days 1 – 4
Doxorubicin  10 mg/m²/day  CIVI*  Days 1 – 4
Cyclophosphamide  400 mg/m²/day  CIVI*  Days 1 – 4
Etoposide  40 mg/m²/day  CIVI*  Days 1 – 4
G-CSF  300 mcg/day SQ  Day 5 until ANC recovery

*Cisplatin, cyclophosphamide and etoposide are to be mixed together in 1000 mL NS and infused continuously over 24 hours on Day 1 – 4. The cisplatin/cyclophosphamide/etoposide are compatible running through a Y–site connector with doxorubicin; **Administer as a 24 hour continuous infusion. Dilute in 250 mL NS; ***Administer thalidomide at bedtime as it can cause somnolence.

Repeat every 4 – 6 weeks.

NOTE: Patients received prophylactic fluconazole, levofloxacin, and acyclovir from the first day of chemotherapy until ANC recovery. *Pneumocystis carinii* pneumonia prophylaxis was also administered.

**DVD (LIPOSOMAL DOXORUBICIN – VINCRI STINE – DEXAMETHASONE)**

Liposomal doxorubicin  40 mg/m$^2$  IV*  Day 1  
Vincristine  1.4 mg/m$^2$  IV**  Day 1  
Dexamethasone  40 mg/day  PO/IV  Days 1 – 4  

*Administer over 1 hour; **Maximum dose is 2 mg.

Repeat cycle every 28 days for a minimum of 6 cycles.


**HyperCVAD (MULTIPLE MYELOMA VERSION)**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose/Media/Method</th>
<th>Time Frame</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclophosphamide</td>
<td>300 mg/m$^2$ Q12H IV*</td>
<td>Days 1 – 3</td>
</tr>
<tr>
<td>Mesna</td>
<td>600 mg/m$^2$/day CIVI**</td>
<td>Days 1 – 3</td>
</tr>
<tr>
<td>Vincristine</td>
<td>2 mg CIVI***</td>
<td>Day 4</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>50 mg/m$^2$ CIVI***</td>
<td>Day 4</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>20 mg/m$^2$/day PO</td>
<td>Days 1 – 5 and 11 – 14</td>
</tr>
<tr>
<td>Vincristine</td>
<td>2 mg IVP</td>
<td>Day 11</td>
</tr>
<tr>
<td>G–CSF</td>
<td>5 mcg/kg/day SQ</td>
<td>Day 6 until ANC recovery</td>
</tr>
</tbody>
</table>

*Administer over 3 hours; **Administer as a continuous infusion over 24 hours; ***Administer as a CIVI over 48 hours. Only administer vincristine and doxorubicin 12 hours after the completion of the last dose of cyclophosphamide.

NOTE: Between Days 8 and 18 all patients received ciprofloxacin, fluconazole, and acyclovir.


**LENALIDOMIDE (REVLIMID*)**

Lenalidomide  25 mg/day  PO  Days 1 – 21  

DOSE MODIFICATIONS: Recommended for neutropenia and thrombocytopenia. Refer to the lenalidomide monograph in the Pharmacology Section.

Repeat cycle every 28 days.

LENALIDOMIDE – DEXAMETHASONE (ECOG E4A03)

Lenalidomide 25 mg/day PO Days 1 – 21
Dexamethasone 40 mg/day PO Days 1, 8, 15, and 22

DOSE MODIFICATIONS: Recommended for neutropenia and thrombocytopenia. Refer to the lenalidomide monograph in the Pharmacology Section. The ECOG protocol required aspirin 325 mg PO QD on days 1 – 28 of each cycle during treatment with lenalidomide and dexamethasone unless the patient was treated with alternative prophylaxis with either low molecular weight heparin or warfarin.

NOTE: This regimen was evaluated in patients with relapsed and refractory multiple myeloma. Routine thromboprophylaxis was not administered to patients in this trial. The thromboembolic events occurred when dexamethasone was added.

Repeat cycle every 28 days for 4 cycles.


LENALIDOMIDE – DEXAMETHASONE

Lenalidomide 30 mg/day PO Days 1 – 21
Dexamethasone 40 mg/day PO Days 1 – 4 every 2 weeks

ONLY in patients with PD/SD disease after 2 cycles of lenalidomide therapy alone

DOSE MODIFICATIONS: Recommended for neutropenia and thrombocytopenia. Refer to the lenalidomide monograph in the Pharmacology Section.

NOTE: This regimen was evaluated in patients with relapsed and refractory multiple myeloma. Routine thromboprophylaxis was not administered to patients in this trial. The thromboembolic events occurred when dexamethasone was added.

Repeat cycle every 28 days.


MP (MELPHALAN – PREDNISONE)

Melphalan 8 mg/m²/day PO Days 1 – 4
Prednisone 60 mg/m²/day PO Days 1 – 4

Repeat cycle every 211 – 282 days.


MP (MELPHALAN – PREDNISONE)

Melphalan 4 mg/m²/day PO Days 1 – 7
Prednisone 40 mg/m²/day PO Days 1 – 7

Repeat cycle every 28 days for 6 cycles.


Last Updated on October 9, 2007
MPT (MELPHALAN – PREDNISONE – THALIDOMIDE)

Melphalan 4 mg/m²/day PO Days 1 – 7
Prednisone 40 mg/m²/day PO Days 1 – 7
Thalidomide 100 mg/day* PO Days 1 onwards

Repeat cycle every 28 days for 6 cycles (melphalan and prednisone only; thalidomide continued until relapse).

*Dose was halved after the occurrence of any non-hematological grade II toxicity.

NOTE: The trial did not initially include anticoagulation prophylaxis. In December 2003, the protocol was amended to include enoxaparin 40 mg/day SQ for the first 4 cycles of treatment. Introduction of enoxaparin prophylaxis reduced the rate of thromboembolism from 20% to 3% (p = 0.005).


THALIDOMIDE

Thalidomide 200 mg/day* PO Daily at bedtime

*Dose increased every 2 weeks for 6 weeks up to a dose of 800 mg/day.


THALIDOMIDE (MAINTENANCE)

Thalidomide 400 mg/day* PO Daily at bedtime

*Dose reductions allowed to a minimum dose of 50 mg/day.

NOTE: Maintenance followed induction VAD chemotherapy for 3 – 4 cycles and began 2 months after autologous stem cell transplantation. All patients received concurrent monthly pamidronate.


THALIDOMIDE – DEXAMETHASONE

Thalidomide 200 mg/day PO Daily at bedtime
Dexamethasone 40 mg/day PO Days 1 – 4, 9 – 12 and 17 – 20

Repeat cycle every 28 days.

NOTE: All patients received monthly bisphosphonate treatment with either pamidronate or zoledronic acid. Patients who developed a DVT or pulmonary embolism stopped thalidomide temporarily, and it was restarted with a 50% dose reduction after therapeutic anticoagulation was achieved. Experts suggest that DVT prophylaxis should be used in all patients starting thalidomide plus dexamethasone. Prophylactic doses of low molecular weight heparin, full-dose anticoagulation with oral warfarin, and aspirin at doses ranging from 81 mg – 325 mg/day have all been effective – see thalidomide monograph for published data.

**THALIDOMIDE – DEXAMETHASONE – LIPOSOMAL DOXORUBICIN (ThaDD)**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Route</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thalidomide</td>
<td>100 mg/day</td>
<td>PO</td>
<td>Daily at bedtime</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>40 mg/day</td>
<td>PO</td>
<td>Days 1 – 4 and 9 – 12</td>
</tr>
<tr>
<td>Liposomal doxorubicin</td>
<td>40 mg/m²</td>
<td>IV</td>
<td>Day 1</td>
</tr>
</tbody>
</table>

Administer in 250 mL D₅W over 1 hour.

Repeat cycle every 28 days.

NOTE: All patients received warfarin 1.25 mg PO QD while receiving thalidomide. Ciprofloxacin 250 mg PO BID was administered to all patients after the initial cohort of patients developed respiratory infections.

DOSE MODIFICATIONS: A 25% dose reduction and a 2 weeks delay in the administration of pegylated doxorubicin occurred when grade 4 mucositis of palmar-plantar erythrodysesthesia occurred. Dexamethasone was reduced to 20 mg PO QD or discontinued in the case of grade 2 and higher muscular toxicity. Thalidomide was only discontinued for Grade 3 neurotoxicity.


**VAD (VINCRISTINE – DOXORUBICIN – DEXAMETHASONE)**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Route</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vincristine</td>
<td>0.4 mg/day</td>
<td>CIVI</td>
<td>Days 1 – 4</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>9 mg/m²/day</td>
<td>CIVI</td>
<td>Days 1 – 4</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>40 mg</td>
<td>IV/PO</td>
<td>Days 1 – 4; 9 – 12 and 17 – 20</td>
</tr>
</tbody>
</table>

*Vincristine and Doxorubicin are admixed in the same bag and infused.*

Repeat cycle every 28 – 35 days.