Multiple myeloma (MM) is a clonal disorder of terminally differentiated B-cells, that is plasma cells. The disease is characterised by a monoclonal gammanopathy, lytic bony lesions, anaemia/bone marrow failure and renal insufficiency. Until recently the treatment of this disease remained unsatisfactory, with patients following a chronic progressive course.1

Over the past decade the approach to patients with MM has changed radically. For over 30 years no therapy was superior to oral melphalan and prednisone (MP).2 However, melphalan led to a complete remission (CR) rate of less than 10% and did not prolong survival beyond 3 years.

On the other hand, high-dose melphalan followed by stem cell rescue leads to CR rates of up to 60% and prolongs overall survival up to 7 years.3 Therefore high-dose therapy has become the treatment of choice for patients with MM world-wide.3

What is the clinical presentation of these patients?

Patients with MM present with various symptoms from bony pain to pathological fractures, symptomatic anaemia, recurrent infections and acute renal failure. The increased protein in the blood may lead to hyperviscosity (Table I).

Two medical emergencies that occur in these patients are hypercalcaemia secondary to the lytic bony lesions and spinal cord compression secondary to vertebral collapse.

The normal age at presentation of patients with MM is generally in the 6th - 7th decade. However, in South Africa, especially in the black population, patients present in their 4th decade. Therefore the diagnosis should be considered in any age group.

How do we make the diagnosis?

In order to make the diagnosis of MM one needs to prove the presence of:
- a monoclonal protein in the serum or the urine
- an increase of plasma cells in the bone marrow or a plasmacytoma, as well as
- one of the following: lytic lesions, anaemia, renal insufficiency or hypercalcaemia.1

Clinical investigations routinely requested if one suspects the diagnosis of MM are the following:
- full blood count
- renal function
- calcium level
- immunoglobulin levels and serum protein electrophoresis
- beta-2 microglobulin
- bone marrow aspiration and biopsy
- skeletal survey
- MRI (to detect very small lytic bony lesions) may sometimes be needed.

What about staging and what is the expected prognosis?

Until recently, traditional staging systems such as the Durie and Salmon system were used for staging patients with MM.4 A more accurate technique called the International Staging System (ISS) for MM has recently been introduced after a multivariate analysis of over 11 000 patients worldwide.4

Three stages were defined based solely on the results of the serum albumin and beta-2 microglobulin (Table II).5

The ISS system also identified two parameters that predicted a poorer outcome: age and high-dose therapy (Table III).5

Who should be treated?

According to the international working group, patients should be divided into asymptomatic and symptomatic. The latter group consists of patients considered for a chemotherapy-based
The disease is characterised by a monoclonal gammanopathy, lytic bony lesions, anaemia/bone marrow failure and renal insufficiency.

### Table II. International staging system for MM

<table>
<thead>
<tr>
<th>Stage</th>
<th>Criteria</th>
<th>Median overall survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Serum B2 microglobulin &lt; 3.5 g/dl</td>
<td>62 months</td>
</tr>
<tr>
<td>II</td>
<td>Neither stage I or stage III</td>
<td>44 months</td>
</tr>
<tr>
<td>III</td>
<td>Serum B2 microglobulin &gt; 5.5 mg/l</td>
<td>29 months</td>
</tr>
</tbody>
</table>

### Table III. Age, chemotherapy, and the international prognostic staging sytem for MM

<table>
<thead>
<tr>
<th>Stage</th>
<th>Median overall survival with high-dose chemotherapy</th>
<th>Median overall survival without high-dose chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age &gt; 65 years</td>
<td>Age &lt; 65 years</td>
</tr>
<tr>
<td>I</td>
<td>111 months</td>
<td>55 months</td>
</tr>
<tr>
<td>II</td>
<td>66 months</td>
<td>40 months</td>
</tr>
<tr>
<td>III</td>
<td>45 months</td>
<td>25 months</td>
</tr>
</tbody>
</table>

intervention. These patients will then be further divided in those who either are or are not candidates for high-dose chemotherapy, followed by stem cell rescue.

Age performance status and co-morbid disease are used to make the decision whether a patient is fit for high-dose therapy. Initially 65 was the upper age limit, but recently high-dose therapy has been delivered to patients beyond the age of 70 years with great success. Therefore most patients should be evaluated by a specialist haematologist or oncologist before they are considered unsuitable for high-dose therapy, as this is currently the only therapy that prolongs survival.

What therapy should be given?

Patients who are candidates for high-dose therapy followed by stem cell rescue will receive induction therapy with high-dose dexamethasone combined with either chemotherapy agents such as vincristine, Adriamycin and cyclophosphamide or with thalidomide, or dexamethasone could be given alone. Currently the most active combination is dexamethasone combined with thalidomide, with response rates of up to 90%.

New agents called proteosome inhibitors are very promising induction therapy agents, but they are currently still under investigation in various clinical trials as first-line therapy.

After around 4 months of induction therapy patients will undergo high-dose therapy followed by stem cell rescue.

It is important to realise that while complete remission prior to stem cell harvesting would be preferred this is often not the case and not mandatory for the treatment plan to continue. Most patients will only have a partial response to the induction chemotherapy.

The next step in the treatment plan is an autologous stem cell harvest which can be done by the combination of chemotherapy and growth factors or by growth factors alone. The stem cells are harvested via an apheresis machine. Most physicians will perform a stem cell harvest large enough to be split into two aliquots in order to provide stem cells for two stem cell transplants. The stem cells are then cryopreserved for further use.

The patients then receive high-dose therapy with melphalan in varying doses, depending on the patient's age. Melphalan is usually used as single agent as it is a very active agent in myeloma therapy and several trials have proven its efficacy with limited toxicity.

Twenty-four hours after the melphalan dose the autologous stem cells are rein fus ed. Melphalan has an extremely short half-life and therefore the cryopreserved stem cells will not be harmed by the melphalan.

This form of transplantation has limited toxicity, with limited cytopenia and a treatment-related mortality of less than 5% in most centres, even in the elderly population. It may be performed on an outpatient basis and this is often the practice in the international arena.

With this procedure patients achieve complete remission rates of up to 50% and if a patient does not attain remission after the first procedure the procedure will be repeated at ± 6 months, even further improving complete remission rates and prolonging overall survival.

After the stem cell transplants all patients will be placed on maintenance thalidomide for an additional 2 years if they can tolerate the therapy.

When patients relapse or progress the newer agents are given as they have been proven to be effective in relapsed refractory patients. The proteosome inhibitors are particularly effective in this group of patients.

Patients who present in their 4th and 5th decade

Although high-dose therapy with melphalan increases complete remission rates and overall survival, most patients will still relapse over time and die from MM. Therefore young patients should always be considered for an allotopic stem cell transplant from a HLA-identical sibling, as this is the only curative treatment for MM at the moment.

Age performance status and co-morbid disease are used to make the decision whether a patient is fit for high-dose therapy.
Multiple myeloma

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to 90%.

Patients who are not candidates
for high-dose therapy
As little as 2 years ago there was general
agreement that the standard of care
for patients who were not eligible
for transplantation, and yet needed
chemotherapy, was MP. Recently, various
randomised trials have shown that,
with the addition of thalidomide to the
combination of MP, complete remission
rates increase dramatically and overall
survival is prolonged. One study even
showed that this combination is superior
to stem cell transplantation.

Unfortunately this combination is not
without increased toxicity and patients
should be placed on anticoagulation due to
a high incidence of thrombotic episodes.
None the less most experts will agree that
MP plus thalidomide is the treatment of
choice for patients who are not candidates
for stem cell transplant.

Other combinations currently under
investigation include combining MP with
the proteosome inhibitors.

Conclusion
Anyone who has treated patients with MM
will agree that the attainment of complete
remission translates into excellent quality
of life. Patients achieving sustained
remission or good partial remission are
asymptomatic for years. They return to
their normal daily activities, lytic bony
lesions resolve and chronic infections
generally clear.

Therefore world-wide the goal of the
treatment of MM has become the
attainment of complete remission.
Thankfully, with high-dose therapy and
the new agents like thalidomide and the
proteosome inhibitors we are obtaining
that goal in the majority of our patients.

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In a nutshell
• Multiple myeloma has a chronic pro-
gressive course if not adequately treat-
ed.
• Standard treatment with melphalan
and prednisone is inferior to current
therapies.
• Thalidomide combined with dexam-
ethasone is the treatment of choice
for induction therapy.
• High-dose melphalan with stem cell
rescue induces high complete remis-
sion rates and prolongs overall sur-
vival.
• Maintenance thalidomide should be
given post stem cell transplant.
• Proteosome inhibitors are currently
reserved for the relapsed refractory
patients.
• Patients who do not qualify for stem
cell transplant should receive melpha-
lan and prednisone combined with
thalidomide.
• Complete remission should be the goal
of therapy.

Therefore world-wide the goal of the
treatment of MM has become the
attainment of complete remission.