Management of multiple myeloma

The approach to the management of multiple myeloma has changed over the past decade.

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Jackie Thomson is a clinical haematologist in the private sector in Pretoria. Her main interest is haematopoietic stem cell transplantation. While studying at Groote Schuur Hospital, her main area of research was transplantation for multiple myeloma.

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.

Table I. Myeloma-related organ or tissue impairment

Criterion	Diagnositic parameter
Hypercalcaemia	Serum calcium > 2.75 mmol/l
Renal insufficiency	Creatinine > 173 mmol/l
Anaemia	Hb 2 g/dl below the lower limit of normal, or Hb < 10 g/dl
Bony lesions	Lytic bony lesions, or osteoporosis with compression fractures
Other associated findings	Symptomatic hyperviscosity, amyloidosis, recurring bacterial infections

The normal age at presentation of patents 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

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Table II. International staging system for MM

Stage	Criteria	Median overall survival
I	Serum B2 microglobulin < 3.5 g/dl	62 months
II	Neither stage I or stage III	44 months
III	Serum B2 microglobulin > 5.5 mg/l	29 months

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

Stage	Median overall survival Age > 65 years	Median overall survival Age < 65 years
I	69 months	47 months
II	50 months	37 months
III	33 months	24 months

Stage	Median overall survival with high-dose chemotherapy	Median overall survival without high-dose chemotherapy
I	111 months	55 months
II	66 months	40 months
III	45 months	25 months

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%.[6] 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.[3]

Twenty-four hours after the melphalan dose the autologous stem cells are reinfused. 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.[3]

After the stem cell transplants all patients will be placed on maintenance thalidomide for an additional 2 years if they can tolerate the therapy.[3]

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 allogeneic stem cell transplant from a HLA-identical sibling, as this is the only curative treatment for MM at the moment.

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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.[7] 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.

References

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In a nutshell

- Multiple myeloma has a chronic progressive course if not adequately treated.
- Standard treatment with melphalan and prednisone is inferior to current therapies.
- Thalidomide combined with dexamethasone is the treatment of choice for induction therapy.
- High-dose melphalan with stem cell rescue induces high complete remission rates and prolongs overall survival.
- 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 melphalan and prednisone combined with thalidomide.
- Complete remission should be the goal of therapy.

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