Summary

Multiple myeloma is a haematopoietic malignancy of terminal differentiated clonal plasma cells. The clinical symptoms are caused by diffuse or multilocular infiltration of the bone marrow with osteolysis and suppression of the normal haematopoesis, as well as by the production of monoclonal immunoglobulins or fragments (light chains or heavy chains).

The International Myeloma Working Group criteria defines myeloma as an **M** protein of **3 g/dL** or higher and/or with clonal bone-marrow plasmacytosis of **10%** or greater, but distinguishes patients with **SMM** from those with symptomatic disease.

Multiple myeloma is a malignant disease characterized by plasmacytosis, paraprotein production, bone lesions, hypercalcemia, anemia, susceptibility to infections, renal impairment abnormalities of the bone marrow microenvironment, and increased osteoclastic activity.

A trend toward a higher incidence of **MM** in patients under age **55** compared with the past **3** to **4** decades has been reported, which implies that important environmental causative factors may have developed in the past **3** to **4** decades. The nature of these and other causative factors in the development of **MM** currently remains unknown.

The presenting features include symptoms of bone disease, typically unexplained backache and sometimes fractures, anaemia, renal insufficiency of different degrees, oedema **(**caused by a nephrotic syndrome and/or cardiac failure**)**, hypercalcaemia, severe bacterial infections and bleeding abnormalities **(**less frequently leucopenia/ thrombocytopenia**)**, peripheral neuropathy and symptoms from hyperviscosity.

Complications of multiple myeloma include renal insufficiency, hematologic complications **(**anemia, bone marrow failure, bleeding disorders) infections, bone complications **(**pathologic fractures, spinal cord compression, hyercalcemia) and neurologic complications **(**spinal cord and nerve root compression, intracranial plasmacytomas, leptomeningeal involvement, among others**)**.

Renal failure is a frequent complication in patients with multiple myeloma that causes significant morbidity. Renal failure is the second most common cause of death in **MM**, surpassed only by infections.

Kidney involvement is seen in **50%** of the patients, but completely different diseases are found Moreover, more than one renal manifestation is often seen in a single patient.

Renal failure in patients with **MM** results from the toxic effects of monoclonal light chains to renal structures, mainly renal tubules, and less often to glomeruli, whereas hypercalcemia is a less common cause of renal insufficiency. The most common finding is cast nephropathy.Other clinicopathological conditions include amyloidosis, light chain deposition disease or acquired adult Fanconi syndrome.These entities may sometimes coexist in the same patient.

Most of the kidney disorders associated with myeloma are caused by the excess production of monoclonal light chains and renal involvement is almost always accompanied by light chain proteinuria. Light chains have variable effects on the kidney; some are more toxic than others.

Factors that are predictive of a recovery of renal function after therapy include previous normal renal function or mild renal insufficiency, the presence of precipitating factors **(*e.g.*.**, dehydration, **NSAID**, hypercalcemia**)**, and early, aggressive treatment.fferent light chains affect different structures in the kidney

Summary

In Some patients, myeloma is diagnosed incidentally because of elevated serum protein levels, but most patients present with symptoms related to anemia, bone lesions, kidney dysfunction, infections, or hypercalcemia. Various blood, urine, bone marrow, and imaging studies are required to diagnose, stage, and monitor the disease and determine prognosis.

diagnosis of **MM** requires **10%** or more plasma cells on bone marrow examination (or biopsy-proven plasmacytoma), **M** protein in the serum and/or urine (except in patients with true nonsecretory myeloma), and evidence of end-organ damage (hypercalcemia, renal insufficiency, anemia, or bone lesions) believed secondary to the underlying plasma cell disorder.

The time-honored Durie-Salmon staging system correlates well with tumor burden.However, the new international staging system, correlates better with prognosis.

The major differential diagnosis includes **MGUS**, smoldering (asymptomatic) **MM**, primary amyloidosis, and solitary plasmacytoma.

The past decade has seen dramatic progress in therapy, three new agents with significant anti-myeloma activity **(**thalidomide, bortezomib, and lenalidomide**)** have been identified.

The main goal of therapy in myeloma is to reduce the level of light-chain production by inducing a remission in the underlying malignancy with chemotherapeutic regimens alone or followed by autologous stem cell transplant **(ASCT)**.

The treatment of myeloma comprises disease-specific therapy and supportive care. The general principle is to reserve disease-specific therapy for active disease.

There is no evidence that starting definitive therapy in patients with smoldering or indolent myeloma improves survival compared with therapy at time of symptoms.

Initial treatment is directed at correcting the reversible factors that contribute to reduced **GFR** and cast precipitation **(**in case of Cast Nephropathy**)**. This includes aggressive hydration **(2** to **3 L/d)**, alkalinization of the urine, discontinuation of **NSAID**, and avoidance of intravenous iodinated contrast media.

Lenalidomide **(**Revlimid**)** plus dexamethasone **(Rev/Dex)** has shown promise, with response rates exceeding **80%** and with lower toxicity than previously observed with **Thal/Dex**. Similar response rates have been observed with bortezomib **(**Velcade**)** plus dexamethasone **(VD)**; bortezomib **(**Velcade**)**, thalidomide, dexamethasone **(VTD)**; and other bortezomib-based combinations.

Although not curative, **ASCT** improves complete response rates and prolongs median overall survival in myeloma with a mortality rate of **1%** to 2%.

For several years, most centres have used peripheral blood stem cells **(PBSC)** instead of bone marrow due to better results, because engraftment is more rapid and there is usually less contamination of the infused cells with tumor cells. **PBSC** can be collected from the peripheral blood after stimulation with granulocyte colony stimulating factor **(G-CSF)** during the regeneration phase after a cytoreductive chemotherapy cycle **e.g**. with cyclophosphamide.

Supportive therapy comprises management of hypercalcemia, skeletal complications, anemia, infections, and pain.

Nonsteroidal anti-inflammatory agents can precipitate renal failure and generally should be avoided. Dehydration, infection, and radiographic contrast media also may contribute to acute renal failure.

Maintenance of a high urinary output **(3 L/d)** is important in preventing renal failure in those with high levels of monoclonal light chains in the urine.

Adequate hydration should be ensured in all patients presenting with renal impairment. Although it has been reported that renal failure could be reverted by high fluid intake alone, hydration alone will at best only slightly reduce the concentration of the pathogenic light chains. Hydration should be combined with antimyeloma treatment, which includes agents that are notexcreted by the kidneys. Additional measures include urine alkalinization and management of hypercalcemia.

Plasmapheresis should be considered in patients with **ARF** in an attempt to prevent irreversible renal failure by avoiding further renal damage.

Plasmapheresis has been used to transiently reduce the plasma concentration of light-chains rapidly in patients with renal insufficiency and it has been recommended in the management of **ARF** in multiple myeloma.

Patients with myeloma and **ESRD** have been treated with hemodialysis and peritoneal dialysis, and they seem to be equally effective, however patients on chronic peritoneal dialysis are at high risk of developing bacterial peritonitis.

The removal of free-light chains with dialysis is another alternative approach, and a new hemodialysis membrane that removes the circulating light chains more efficiently has been recently developed. A small study investigating hemodialysis with a protein-leaking dialyzer indicated that large reductions in the concentration of serum-free light chains could be obtained.

Renal transplantation has not been considered a viable option in most patients with multiple myeloma because of their poor prognosis.

however, patients with stable disease have received cadaveric renal transplants that survived **>12 mo (**range **14** to **144 mo)** without recurrence of myeloma kidney.