Advances in myeloma diagnosis and treatment

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Multiple myeloma may be incurable but treatment in the last decade has improved median survival from 36 to 54 months, following the introduction of high dose therapy. This approach, along with several new classes of drugs, means that around 40% of newly diagnosed patients will survive 10 years or more. The full impact of these novel agents may yet to be realised once they are incorporated into frontline therapy.

Presentation varies

Multiple myeloma may be difficult to diagnose due to its non-specific presentation. Symptomatic myeloma, the basis for recommending treatment, usually involves one of the CRAB criteria (hyperCalcaemia, Renal impairment, Anaemia, Bone pain / lytic lesions), which in turn implies end-organ damage.

On the other hand, patients with a paraprotein and no CRAB features can be carefully monitored without intervention, thus avoiding treatment while not compromising long-term outcome.

Generalised skeletal involvement leads to bone pain, lytic lesions, pathologic fracture, anaemia and hypercalcaemia. The anaemia of myeloma is due to bone marrow infiltration and suppressed erythropoietin production secondary to renal impairment.

Renal impairment, present in 20% of cases at diagnosis, is associated with a poorer prognosis. Renal damage occurs because of the direct toxic effect of light chains and hypercalcaemia, the effect of drugs (especially NSAIDs and some antibiotics) and dehydration. These factors should be rapidly corrected or avoided.

Bacterial infection is the leading cause of death in newly diagnosed patients. Risk factors include neutropenia, pain, chemotherapy and vascular access devices.

Laboratory diagnosis

The plasma cells of multiple myeloma are terminally differentiated B cells, which means they almost always produce either intact immunoglobulin (75% of cases), or light chains (24%), while some cases produce both and a few have no detectable paraprotein.

Serum protein electrophoresis (SPE) will quantify a paraprotein in 75% of cases and immunofixation electrophoresis identifies the immunoglobulin isotype (IgG, IGA, IgD, IgM or IgE). Changes in paraprotein level are used to monitor both response to therapy and the detection of relapse.

Urinary Bence Jones protein (BJP) seen with light chain myeloma has several limitations for either myeloma detection or monitoring. Urine collection can be problematic, and early in the disease light chains may not appear in the urine because the kidney has huge resorptive capacity – they only appear when this capacity is exceeded or there is renal impairment. This can delay diagnosis as well as limit monitoring for response to therapy or to detect a relapse.

The extremely sensitive serum free light chain assay has overcome some of these problems. It detects light chains into the normal range and the ratio of kappa-lambda light chains is used to imply monoclonality. Where there is renal impairment, light chains are retained but the kappa-lambda ratio is unaffected.

The major advantages of light chain assay are:

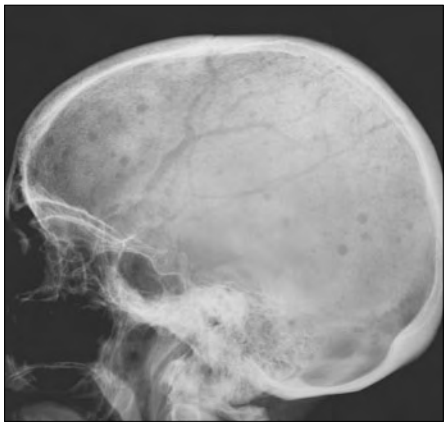
- A single serum sample for both SPE and light chain assay.
- More accurate myeloma diagnosis and monitoring i.e. assay levels relate to tumour activity not renal function. This is particularly important for detecting complete remission, which is associated with improved survival and should be the aim of therapy.
- In so-called non secretory myeloma, up to 80% of patients have an abnormal serum free light chain ratio, allowing easy monitoring that previously did not exist.
- Combined with SPE, the tests together detect 99% of cases of myeloma (compared with 95% if BJP is used).

Treatment

High dose therapy with autologous stem cell rescue was introduced routinely in the mid 1990s. This therapy is current standard of care for younger patients who can withstand treatment, giving it safety (mortality 1.5%) and efficacy, with better response and long term outcome than conventional chemotherapy.

Thalidomide was introduced to myeloma therapy in 1999, based on observed anti-angiogenesis effects, and clinically relevant responses were observed in around 30% of heavily pre-treated patients. This response was enhanced when combined with dexamethasone. Ongoing studies indicate that thalidomide combined with chemotherapy induces improved responses in elderly patients in particular; better than stem cell transplantation and now considered standard therapy in combination with melphalan and prednisolone for these patients. Recently licensed for frontline therapy in Australia, thalidomide's common side effects are peripheral neuropathy, severe constipation, and somnolence, with a significant risk of DVT that requires some prophylaxis at treatment onset e.g. aspirin.

Bortezomib (Velcade™) is a proteosome inhibitor that has achieved responses of 30-40% in heavily pre-treated patients, again the effect being enhanced with added dexamethasone. Side effects include peripheral neuropathy and increased risk of DVT.



Skull x-ray showing typical multiple punched out lesions (photo courtesy www.imagingpathways.health.wa.gov.au)

Thrombocytopenia is almost universal though this tends to improve with subsequent cycles of bortezomib, although platelet support may be required with initial use.

Lenalidomide is a more potent thalidomide analogue with unknown action; anti-angiogenesis, enhanced production of tumor necrosis factor and other cytokines, and direct anti-myeloma affect are all thought to play a role. Response rates in relapsed patients are similar to bortezomib and thalidomide. Its major advantage is a marked reduction in peripheral neuropathy. Major side effects are haematological, with peripheral blood cytopenias that can be readily managed.

Maintenance therapy

Maintenance therapy post stem cell transplant is designed to improve the response rates and for those in complete remission to achieve even deeper responses.

Thalidomide use after high dose therapy does achieve these outcomes, which translates into improved progression-free and overall survival. Optimal therapy spans about 6-9 months. Further studies will assess the role of the other agents for consolidation/maintenance therapy.

The future

The novel agents are currently only available for relapsed disease. There is mounting evidence that improved response rates and in particular, complete remissions, are associated with improved long term outcomes. These agents are capable of achieving such responses. The future challenge is to support ongoing clinical and translational research that fully exploits the potential of these drugs. In Perth, combination therapy with bortezomib followed by high-dose therapy is available as part of a clinical trial. ■