Diagnosis and treatment of multiple myeloma

Diagnosis

In patients with predominant production of light chains, the concentration of the complete immunoglobulin molecule is often too low to result in an easily detectable M-component in the serum electropheresis, hampering early diagnosis of myeloma. The great majority of paraprotein is secreted as λ light chain, which is filtered through the glomerular apparatus and excreted by the kidneys. Urine electropheresis is mandatory because the differential diagnosis should consider monoclonal gammopathy of unknown significance (MGUS), smouldering myeloma, extramedullary and solitary plasmacytoma, and amyloidosis. Patients with MGUS and those with primary amyloidosis lack the skeletal lesions typical of myeloma and have less than 10% bone marrow plasma cells. In MGUS, the paraprotein concentration is less than 3g/l and patients are asymptomatic. The prognosis of patients depends on various factors, among which age, International Staging System tumor stage, and cytogenetic factors are most important.

Massive proteinuria is seen in other conditions such as amyloidosis or nephritic syndrome as well. In these disorders, albumin is the predominantly excreted protein, while in light chain myeloma, Bence–Jones protein constitutes the vast majority of the urinary protein and is easily detected as a massive M-spike. Nevertheless, confirmation of the paraprotein by immunolectropheresis is required. Myelomatous bone lesions predominantly manifest in the lower thoracic and in the lumbar spine. MRI of the spine is the most sensitive technique for detection of osteolytic lesions, fractures, and diffuse marrow infiltration by myeloma cells, and is superior to conventional radiography. Detection of ‘punched out’ osteolytic lesions without surrounding osteoblastic bone formation is typical of myeloma and generally rules out bone metastases of other tumors such as breast, bronchial or kidney cancer. Myeloma cells are usually easily distinguished from other bone marrow cells by their typical morphologic appearance, but nowadays more sophisticated techniques such as immunophenotyping are applied to distinguish between clonotypic and polyclonal plasma cells. The proportions of these two types of cells is prognostically relevant in plasma cell dyscrasias; the greater their percentage in the monoclonal pool, the poorer the patient’s outlook. Cytogenetic investigation of isolated $CD138^+$ myeloma cells by fluorescence *in situ* hybridization technology is used to improve predictions of prognosis in individual cases. Patients with chromosomal abnormalities such as t(4;14), t(4;16), t(4;20), del 17p and abnormalities of 1q21 have a dismal prognosis and re-

duced sensitivity to conventional cytostatic drugs and thalidomide. The same applies to those with del 13q detected by conventional cytogenetics.

Patients with primary amyloidosis present with monotypic circulating free light chains either as the sole finding or in combination with a monotypic complete immunoglobulin molecule with excess levels of the same light chain class. Amyloidosis results in the deposition of amyloid fibrils in several organs and tissues leading to severe organ failure. Patients with smouldering myeloma present with paraprotein of >3 g/l, significant bone marrow plasma cell infiltration (>10%) without major bone lesions, and are asymptomatic. Plasmacytoma must be distinguished from multiple myeloma, which shows disseminated disease, whereas plasmacytomas present with no or only minimal diffuse bone marrow infiltration. Extramedullary plasmacytoma usually originates from lymphatic tissue of the upper airways and is potentially curable; the median age at presentation is around 55 years. By contrast, solitary plasmacytoma originates from lymphatic cells located in the skeleton and can be curable by local treatment (surgery and/or radiotherapy) provided the disease did not disseminate. The median age at manifestation is around 60 years.

Treatment

Treatment is withheld in asymptomatic patients (smouldering myeloma) and only recommended in those with ‘active’ myeloma, meaning that patients must present with one or more ‘CRAB’ criteria (hypercalcemia, renal impairment, anemia, bone disease).[1]

Renal impairment is frequently the consequence of direct damage of renal tubular cells by pathogenic light chains complexed with Tamm–Horsfall protein. The proteins aggregate with cell debris to form tubular casts, which result in tubular damage, distention and obstruction. In response to inflammatory stimuli, mononuclear cells migrate into renal tissue where they lead to interstitial inflammation and scar formation. This type of renal injury must be distinguished from renal damage caused by other light chains with a tropism for either mesangial cells or proximal tubuli. Glomerulopathic light chains may lead to amyloidosis or light chain deposition disease, whereas other (rare) tubulopathic light chains may result in Fanconi syndrome. These light-chain-induced complications must be clearly distinguished from renal problems arising from conditions common in patients with myeloma, such as application of contrast media, hypercalcemia, infections, dehydration, and treatment with nephrotoxic drugs such as NSAIDs or antibiotics.

In the circumstance of eventual relapse, several treatment options can be considered. In case of a long interval between initial therapy and relapse, retreatment with the first-line protocol or, in case of an initial autologous transplantation, a second autologous transplantation would be a valuable choice. Otherwise, combination treatment using bortezomib or lenalidomide might be applied, or treatment combinations including thalidomide, alkylating agents or one of the new drugs in clinical testing, such as carfilzomib, vorinostat or pomalidomide.

1. International Myeloma Working Group. Criteria for the classification of monoclonal gammopathies, multiple myeloma and related disorders: a report of the International Myeloma Working Group. *Br. J. Haematol.* **121**, 749–757 (2003).