Immunoproliferative Disorders

28

Contents

Abstract

Multiple myeloma (MM) is a B-cell neoplastic disease characterized by excessive number of abnormal plasma cells in the bone marrow and overproduction of intact monoclonal immunoglobulins or light chain (Bence Jones) proteins. The average age of onset is about 60 years and occurs more frequently in men than women. MM is preceded by a premalignant condition termed monoclonal gammopathy of undetermined significance (MGUS). Age is an important prognostic factor, and with each decade from the age of 50 years to over the age of 80, the overall survival declines. This review will provide an update on the clinical management of multiple myeloma.

Keywords

Multiple myeloma · Monoclonal gammopathy of undetermined significance (MGUS) · Bence Jones proteins · B-cell neoplastic disease

Introduction

Multiple myeloma is a B-cell neoplastic disease characterized by excessive number of abnormal plasma cells in the bone marrow and overproduction of intact monoclonal immunoglobulins or light chain (Bence Jones) proteins.The cause is not known and the epidemiological pattern remains obscure [1]. Age is the most significant risk factor. Genetic factors, certain viruses, certain chemicals and radiation and certain occupations have been suggested as possible associations in its causation. It is possible that many factors acting together result in myeloma.

Clinical Manifestations

The average age of onset is about 60 years and occurs more frequently in men than women. Because of its effects on the bone, bone marrow and kidney,

N. Nagaratnam et al., *Geriatric Diseases*,
https://doi.org/10.1007/978-3-319-33434-9_25

the clinical features are osteolytic lesions, anaemia, renal insufficiency and recurrent bacterial infections [2] (Box 1). Physical examination reveals pallor, bone tenderness, ecchymosis, papules, nodules, neurological deficits, extramedullary plasmocytomas and amyloidosis (macroglossia, shoulder pad sign – bilateral swelling of the shoulder joints due to deposition of amyloid). X-ray of the bones may show typical punched-out lytic lesions (Fig. 1) or diffuse generalized osteoporosis. MM patients are prone to develop deep vein thrombosis and venous thromboembolism [3]. About one-fifth of the patients at the time of diagnosis will have renal insufficiency, and about half over the course of the disease will have renal dysfunction [4, 5].

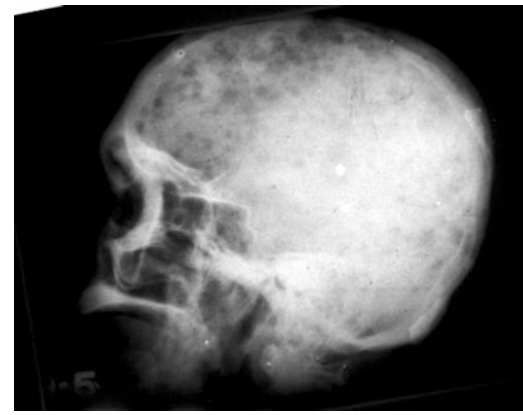

Fig. 1 Lateral view of the skull with changes due to multiple myeloma showing numerous punched-out osteolytic areas

Box 1 Clinical Symptoms of Multiple Myeloma

Bone

- Pain, pathological fractures
- Localized tumours (plasmocytomas)

Blood

- Bleeding manifestations
- Hypercalcaemia
- Hyperviscosity

Renal insufficiency

Neurological

- Spinal cord compression
- Carpal tunnel syndrome
- Peripheral neuropathy

Infection

- Bacterial (recurrent)

Information sources: [2, 4, 5].

MM is preceded by a premalignant condition termed monoclonal gammopathy of undetermined significance (MGUS) [6]. MGUS is marked by the presence in the serum of less than 30 g/l of monoclonal IgG and IgA without any other evidence of multiple myeloma, i.e. bone marrow plasmacytosis, lytic bone lesions and decreased levels of normal immunoglobulins. Long-term follow-up (for 30 years or more) of patients have shown that multiple myeloma develops in up to 16% with an annual actual risk of 0.8% [7].

Diagnosis

The basic tests include a full blood count, creatinine, uric acid, electrolytes and sedimentation rate. All patients are screened with electrophoresis of serum and urine. Immunofixation of the paraprotein band enables to identify the immunoglobulin isotype of the paraprotein. Bone scanning lacks specificity for myeloma and is not a suitable alternative for radiological examination [8]. Bone marrow aspiration is a decisive procedure in establishing a definite diagnosis of myeloma (Fig. 2). The criteria for the diagnosis of MM is based on the clinical manifestations of end organ damage and is referred to as CRAB [4]: (i) hypercalcaemia, a serum calcium level more than 2.75 mmol/L; (ii) renal insufficiency, creatinine more than 173 mmol/L; (iii) anaemia, haemoglobin less than 10gm/dL; and (iv) bone lesions [4].

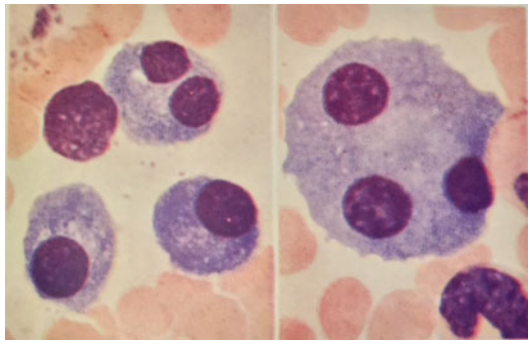

Fig. 2 Bone marrow showing polypoid plasma cells. Reproduced with kind permission from Norvatis Company Archives, *Sandoz Atlas of Haematology* FA Sandoz,1973

Prognosis

Age is an important prognostic factor, and with each decade from the age of 50 years to over the age of 80, the overall survival declines [9]. The total mass of myeloma cells correlate directly with the bone lesions, hypercalcaemia and anaemia and have prognostic value [10, 11]. In unselected patients, the prognosis is 2.5–3 years (median survival) [12]. A Mayo Clinic study revealed that plasma cell labelling index, levels of thymidine kinase, beta-2 macroglobulin, serum albumin and C-reactive protein and age were significant univariate prognostic factors [12]. Beta-2 microglobulin is a strong predictor of outcome and a marker for the overall body tumour burden. Beta-2 microglobulin and C-reactive protein together have been used to estimate prognosis in terms of median survival. If both levels are below 6 mg/l, the survival is 54 months; if one component is less than 6 mg/l, it is 27 months; and if both are greater than 6 mg/l, it is 6 months [13]. CRP is useful to gauge prognosis as CRP is a surrogate marker of interleukin-6 and is often referred to as plasma cell growth factor [13] Serum immunoreactive IL-6 is a significant prognostic marker in multiple myeloma, and high level is regarded as a predictor of poor prognosis [14]. It should be noted, however, that beta-2 microglobulin may be raised in renal failure and C-reactive protein may be raised due to infective or inflammatory disorders. Myeloma can be staged using the Durie–Salmon staging system [15] which is divided into three stages – low-, intermediate- and high-class cell mass – and based on the severity of the anaemia, calcium level, renal failure, presence or absence of bone lesions and the quantity of abnormal proteins using clinical parameters that predicted myeloma cell tumour burden. It is useful as a measure of prognosis. The International Staging System for multiple myeloma relies mainly on the level of albumin and beta-2 microglobulin and is regarded as a simple and reliable predictor of survival duration [16–19]. Cytogenetic data contributes to significant prognostic information although the yield is low [3].

Treatment

In patients without comorbidities (cardiovascular or significant renal impairment) and under 65 years of age, the aim of treatment is to improve survival with an autograft which consists of a 3–6 months of induction therapy aimed at reducing tumour load and contamination of stem cell harvests by malignant cells [20] followed by autologous stem cell transplantation (ASCT). A second stem cell transplantation 3–6 months after the first is given for those who did not have a full response to the first [21] (Fig. 3). Patients who are very much older and with significant comorbidities may be treated with oral chemotherapy (melphalan or cyclophosphamide and prednisolone). However, ASCT is practical in selected patients older than 65 years with good functional status without severe comorbidities [23]. Novel therapeutic agents (immunomodulatory drugs thalidomide and lenalidomide and protease inhibitor bortezomib) are now increasingly used in the treatment of MM and the superiority of adding one novel agent to melphalan plus prednisone [22]. Randomized controlled trials show that in the elderly who are not eligible for transplant, the addition of thalidomide to melphalan and prednisolone results in response rates superior to melphalan and prednisolone alone [23]. Recent studies have shown a good response in a high

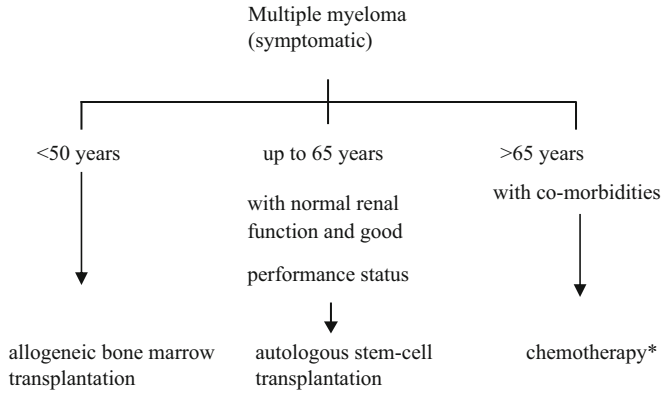

Fig. 3 Treatment of multiple myeloma based on age and comorbidities (Information source: Attal et al. [25]; Harousseau [22])

proportion of patients treated with targeted therapies.

New targeted drug therapies include three drugs: thalidomide, its analogue lenalidomide and the proteasome inhibitor bortezomib [24]. Neuropathy is a major side effect with thalidomide and bortezomib and myelotoxicity with lenalidomide [24]. Thalidomide and dexamethasone have been shown to be as effective for induction before stem cell transplantation as standard therapies [24]. Thalidomide taken after stem cell transplantation prolongs event-free survival and prevents relapse as compared with no therapy [25]. Treatment with interferon alfa is controversial.

Lytic bone disease, bone pain and hypercalcaemia are common clinical manifestations of myeloma. Myelomatous bone disease can be treated or even prevented with bisphosponate therapy. An uncommon side effect of this agent is osteonecrosis of the jaw [24, 26, 27] (Fig. 3).

Impact

See ▶ Chap. 29, "Lymphoproliferative Disorders"; Box 2

Box 2 Key Points. Multiple Myeloma

Because of its effects on the bone, bone marrow and kidney, the clinical features are osteolytic lesions, anaemia, renal insufficiency and recurrent bacterial infections [2].

Box 2 Key Points. Multiple Myeloma (continued)

Age is an important prognostic factor, and with each decade from the age of 50 years to over the age of 80, the overall survival declines [9].

Patients who are very much older and with significant comorbidities may be treated with oral chemotherapy (melphalan or cyclophosphamide and prednisolone).

However, ASCT is practical in selected patients older than 65 years with good functional status without severe comorbidities [23].

New targeted drug therapies include three drugs: thalidomide, its analogue lenalidomide and the proteasome inhibitor bortezomib [24].

Multiple Choice Questions

1. A 70-year-old man complained of fatigue, tiredness, weakness and low back pain over 3–4 months. Routine blood smear showed normocytic normochromic anaemia with rouleaux formation. The sedimentation rate was markedly increased. The diagnosis was multiple myeloma.

   The following would be consistent with the patient's illness, except:

   A. Beta-2 microglobulin is elevated.
   B. X-ray of bones shows generalized osteoporosis.

C. Serum level of monoclonal protein is >30 g/L.
D. Serum electrophoresis shows polyclonal pattern.

2. The following are associated with paraproteinaemia, except:
A. Chronic granulocytic leukaemia
B. Chronic lymphatic leukaemia
C. Primary amyloidosis
D. Macroglobulinaemia

MCQ Answers

1 = D; 2 = A

Short Answer Questions

1. List four clinical and laboratory findings for the diagnosis of multiple myeloma.

SAQ Answers

1. Peak incidence between 60–70 years
2. Blood marrow plasmacytosis of >10%
3. Multiple osteolytic lesions on X-ray
4. Bence Jones proteinuria

References

1. Riedel DA, Pottern LM. The epidemiology of multiple myeloma. Haemat Oncol Clin North Am. 1992;6:225–47.
2. Kyle RA. Multiple myeloma: review of 869 cases. Mayo Clin Proc. 1975;50:29–40.
3. Jagannath S. Pathophysiological underpinnings of multiple myeloma progression. J Managed Care Pharm Supplement. 2008;14(7):S7–S11.
4. Katzel JA, Hari P, Vesole DH. Multiple myeloma: charging toward a bright future. CA Cancer J Clin. 2007;57:301–18.
5. Dimopoulos MA, Kastritis E, Rosinol L, Blake J, Ludwig H. Pathogenesis and treatment of renal failure in multiple myeloma bone disease. Haematol Oncol Clin North Am. 2007;21:1035-1-9.
6. Anderson KC,Carrasco RD. Pathogenesis of myeloma. Annual Rev Pathol Mech Dis. 2011;6:24.
7. Kyle RA. "Benign" monoclonal gammopathy-after 20–35 years of follow up. Mayo Clin Proc. 1993;68:26–36.
8. Firkin F. Screening for multiple myeloma. Aust Prescriber. 2009;32:92–94.
9. Ludwig H, Bolejack V, Crowley J, Blade J, San Miguel J, Kyle RA. Survival and years of life lost in different age cohorts of patients with multiple myeloma. J Clin Oncol. 2008;28:1599–160.
10. Alexanian RA, Balcerzak S, Bonnet JD, Gehan E, Haut A, Hewlett JS, et al. Prognostic factors in multiple myeloma.Cancer.1975;36:1192–201.
11. Durrie BGM, Salmon SE, Moon TF. Pretreatment tumour mass, cell kinetics and prognosis in multiple myeloma. Blood. 1980;55:364–72.
12. Kyle RA. Prognostic factors in multiple myeloma. Stem Cells. 1995;13 Suppl. 2:56–63.
13. Bataille R, Boccadoro M, Klein B, Durie B, Pileri A. C-Reactive protein and beta-2 microglobulin produce a simple powerful myeloma staging system. Blood 1992;80(3):733–7.
14. Pelliniemi TT, Irjala K, Mattila K, PalkkiK, Rajamaki A, Tienhaara A, et al. Immunoreactive interleukin-6 and acute phase proteins as prognostic factors in multiple myeloma. Finnish Leukaemia Group. Blood. 1995;85(3):765–71.
15. Durie BGM, Salmon SE. A clinical staging system for multiple myeloma. Cancer. 1975;36:842–854.
16. Greipp PR, Miguel JS, Durie BGM, Crawley JJ, Barlogie B, Blade J, et al. International staging system for multiple myeloma. J Clin Oncol. 2005;23(15):3412–3420.
17. Cassuto JP, Krebs BJ, Vit G. Beta-2 microglobulin a tumour marker of lymphoproliferative disorders. Lancet. 1978;2:108–109.
18. Bataille R, Durrie BGM,Grenier J. Serum beta 2 microglobulin and similar markers in multiple myeloma : a reliable marker for staging. Br J Haematol. 1093;55:439–44.
19. Norfolk D,Child JA, Cooper EH, Kerruish S,Ward AM. Serum beta-2 microglobulin in myelomatosis. Potential value in stratification and monitoring. Br J Cancer. 1980;42(4):510–515.
20. Attal M, Haroussaue JL, Stoppa A M, Sotto JJ, Fuzibet JG, Rosal JF, et al. A prospective randomized trial of autologous bone marrow transplantation for multiple myeloma. Intergroupe Francais du Myeloma. N Engl J Med. 1996;335:91–97.
21. Attal M, Harousseau JL, Facon T, Guilhot F, Doyen C, Fuzibet J-O, et al. Intergroupe Francophone du Myelome. Single versus double autologous stem-cell transplantation for multiple myeloma. N Engl J Med. 2004; 350:1655–1664.
22. Hoarousseau J-L. Multiple myeloma in the elderly: When to treat. Whe to go to transplant. 2010. http://www.cancernetwork.com/mulitiple-myeloma/multiple-myeoma-elderly –when -treat.
23. Osborn M, Horvath N, To LB. New drugs for multiple myeloma. Aust Prescriber. 2009;32:95–98.
24. Joshua DE. Multiple myeloma: the present and the future. AJA. 2005;183:34418.

25. Attal M, Harousseau JL, Leyvraz S, Doyen C, Hulin C, Benbonbker L, et al. Maintenance treatment with thalidomide and pamidronate after autologous transplantation for myeloma: second analysis of a prospective randomized study of the Intergroupe Francophone du Myeloma. Haematologica. 2005;90 Suppl 1:17.
26. Roodman GD. Mechanisms of bone metastasis. N Engl J Med. 2004:350:1655–1664.
27. Berenson JR, Rosen LS, Howell A, Porter L, Coleman RE, Morley N, et al. Zoledronic acid reduces skeletal –related events in patients with osteolytic metastases. Cancer. 2001;91:1191–1200.