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Review

Managing multiple myeloma in the over 70s: A review

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ABSTRACT

Multiple myeloma (MM) remains an incurable malignancy. Approximately 37% of patients with plasma cell myeloma are over the age of 75 and the median age of diagnosis is 70. The management approach to over 70s differs from younger patients, as treatment goals may vary and underlying co-morbidities and expected treatment related toxicities have to be taken into account. Individualisation of management is important, aiming to achieve the best response whilst minimising adverse events. A proportion of patients will be unable to tolerate any treatment with palliation being appropriate. Age alone should not be a barrier to treatment however, with some fit patients over the age of 70 potentially benefitting from intensive treatment options including high dose chemotherapy with autologous stem cell rescue. Comprehensive geriatric assessment is indicated in the over 70s; this should be employable in a clinic outpatient setting to make it feasible. Outcomes of this assessment potentially help physicians' choice of therapy. For decades the combination of Melphalan and prednisolone was the standard of care for older MM patients. Over the last ten years, newer drugs and combinations have improved therapeutic options for patients but are yet to demonstrate vast improvement in overall survival in this cohort.

Contents

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1. Introduction

Plasma cell myeloma is a neoplastic disorder characterised by clonal proliferation of malignant plasma cells within the bone marrow [1]. In Western countries, the annual age-adjusted incidence is 5.6 cases per 100,000 people with the median age at diagnosis being 70 years and a third of patients being more than 75 years [2]. There is almost always a monoclonal protein band present in the blood or urine (only 2% of cases are "non-secretory") and there has to be evidence of organ dysfunction to diagnose symptomatic MM [3]. MM is diagnosed according to the recently revised International Myeloma Working Group (IMWG) criteria [4] detailed in Table 1.

It is now clearly recognised that myeloma is preceded by an asymptomatic monoclonal gammopathy (MGUS) phase in all patients [5]. MGUS is common, with a monoclonal protein being present in 1–2% of people in their sixth decade, 2–4% in their seventh decade and 4–5% in their eighth decade [6]. On average, the annual risk of transformation to symptomatic multiple myeloma is 1% a year. These patients require monitoring, typically every 6–12 months, which can usually be carried out in primary care with specialist haematology input as required [7].

Over the last decade, the introduction of novel agents such as the immunomodulatory drugs (IMiDs), thalidomide and lenalidomide and the proteasome inhibitor bortezomib has changed the treatment landscape of myeloma and extended overall survival [8]. However, this benefit appears to be confined to the young, with no difference in survival between 1990–1992 and 2002–2004 for those over the age of 70 (5-year relative survival: 27–29%; [9]). This may partly be explained by myeloma biology with older patients having less favourable prognostic features, although they do not have an increased rate of adverse cytogenetic abnormalities [10]. Perhaps more importantly, the human ageing process is associated with a gradual progressive decrease in physiological reserve. Ageing is associated with clinically significant reductions in renal function, hepatic mass and blood flow, bone marrow status and cardiovascular function [11–14]. These changes affect the pharmacokinetics and pharmacodynamics of administered drugs, altering clinical efficacy and potentially increasing toxicity.

In this review, we lay out our approach to the diagnosis and management of patients over the age of 70 with a new diagnosis of myeloma.

1.1. Presenting features and investigations

Presenting features of myeloma include unexplained anaemia, bone pain, hypercalcaemia, impaired renal function, spinal cord compression, recurrent bacterial infections and rarely, symptoms of hyperviscosity. Spinal cord compression, acute kidney injury and hypercalcaemia are medical emergencies requiring urgent hospitalisation. More commonly however, patients present in an insidious fashion, typically with bone pain, anaemia and mild renal dysfunction. There is often a delay between symptom onset and diagnosis with the average duration being around 6 months [15]. This may be particularly pronounced in the elderly where early non-specific symptoms such as fatigue, bone pain and susceptibility to infections may be attributed to other causes.

The investigations normally undertaken are outlined in Table 2. ^{18}-F FDG PET/CT appears to have an emerging role in staging myeloma [16]; but is currently regarded as a research tool and rarely used in routine practice. There should be a low threshold for whole spine Magnetic Resonance Imaging (MRI) in proven cases of myeloma with back pain as this can help guide painful areas suitable for radiotherapy or vertebroplasty and assess spinal cord or nerve root damage. In the very elderly, a personalised approach is necessary with some of the more onerous investigations being omitted depending upon co-morbidities or frailty. Patients are routinely staged according to the International Staging System (ISS) for myeloma using a combination of albumin and β2-microglobulin, which is associated with overall prognosis [17]. Certain cytogenetic abnormalities are associated with poor prognosis including deletions of chromosome 17p (TP 53 deletion), t(4:14) and t(14:16) and these should be assessed by Fluorescent in situ Hybridisation (FISH) at diagnosis [3].

1.2. To treat or not to treat?

Symptomatic myeloma is diagnosed based on the "CRAB" criteria comprising hypercalcaemia, renal dysfunction, anaemia and bone lesions (Table 1; [4]). Disease specific therapy is required promptly in such situations to either halt or reverse organ dysfunction.

There is no evidence that early treatment in most cases of asymptomatic myeloma (that is, patients who meet the diagnostic criteria in terms of their paraprotein or plasma cell percentage but without "CRAB") is beneficial and close monitoring is appropriate in such cases under the supervision of a consultant haematologist [18]. Such patients have a 50% risk of needing treatment over 5 years [19]. Recently it has been recognised by the IMWG that a group of ultra high risk patients with asymptomatic multiple myeloma exists (Table 1; [4]). Such patients inevitably progress to symptomatic multiple myeloma and early treatment is therefore felt beneficial.

A difficult and common scenario occurs in patients with age related organ dysfunction due to reasons other than myeloma. Age-related osteoporosis is common; there should therefore be a high threshold for labelling patients with symptomatic multiple myeloma based upon osteoporosis alone without lytic lesions or evidence of other organ damage. Similarly, chronic kidney disease (CKD) (usually due to hypertension or diabetes is present in 30–50% of cases) over the age of 70 [20] so initiating therapy is not always necessary. Rarely, a renal biopsy may be required. If anaemia seems out of proportion to the disease burden, concurrent causes including haematinic deficiency, chronic inflammation or even myelodysplastic syndrome should be sought. Finally, primary hyperparathyroidism which is associated with mild hypercalcaemia has a prevalence of about 0.2% in the over 70s [21].

1.3. Assessment of elderly patients

It is clear that age alone can no longer be considered the only criterion on which to choose treatment. In an elderly MM patient, frailty, ongoing co-morbidities and disability should all be assessed prior to choice of therapy. The Eastern Co-operative Oncology Group score (ECOG; [22]) is still the most widely used assessment of functional status (Table 3) and is often used to guide therapy.

However, this is less suited to the geriatric population: 9–38% of elderly patients with a good performance status (<2) are partially or fully independent on others to carry out ordinary activities such as household tasks and personal care [23,24]. Many prognostic indices for the elderly that incorporate age, comorbidity or both are available; the Charlson comorbidity index is most frequently used in patients with cancer and has been validated in myelodysplastic syndrome [24,25]. To date no myeloma studies have prospectively assessed outcomes in patients with varying abilities and co-morbidities. Until such data become available, chemotherapy doses are often empirically dose attenuated and patients require close follow-up. Clinical judgement is necessary combined with discussion with the multidisciplinary team taking into account patient choice.