

Guidelines on the diagnosis and management of solitary plasmacytoma of bone, extramedullary plasmacytoma and multiple solitary plasmacytomas: 2009 update

Prepared by a working group of UKMF Guidelines Working Group

M. Hughes, R. Soutar, H. Lucraft, R. Owen, J. Bird

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Address for correspondence

Dr Marie Hughes
Consultant Haematologist
Department of Haematology
Falkirk and District Royal Infirmary
Majors Loan
Falkirk
FK1 5QE
01324 624000 Ex 5408
marie.hughes@nhs.net

Introduction

Guidelines on the diagnosis and management of solitary plasmacytoma of bone (SBP) and extramedullary plasmacytoma (EP) were published on behalf of the UK Myeloma Forum and British Committee for Standards in Haematology in 2003(1). This update incorporates newly available information on diagnosis, prognosis and management and includes a new section on the management of multiple solitary plasmacytomas (+/-recurrent).

A literature search was performed using MEDLINE and EMBASE from 2002 to November 2008. A search was made for randomised controlled trials involving plasmacytoma, papers where plasmacytoma was the major focus of the paper and reviews where plasmacytoma was the major focus. SBP and EP remain rare diseases and most of the evidence relates to retrospective data from patient series collected over long periods of time. Very few formal clinical trials exist. The majority of the recommendations given therefore remain consensus of expert opinion. Criteria used to quote levels and grades of evidence are as in Appendix 3 of the Procedure for Guidelines Commissioned by the BCSH (<http://www.bcshguidelines.com>).

Definitions

In 2003 the International Myeloma Working Group (IMWG) published criteria for the classification of monoclonal gammopathies, multiple myeloma and related disorders recognising solitary plasmacytoma of bone, extramedullary plasmacytoma and multiple solitary plasmacytomas (+/- recurrent) as distinct entities (2). The diagnostic criteria are listed in Table 1. The World Health Organisation published a similar classification system for plasma cell dyscrasias in 2001 recognising solitary plasmacytoma of bone and extramedullary/extraosseous plasmacytoma (3).

Solitary plasmacytoma of bone

Context

Since the previous guideline several new articles on prognostic factors, treatment and outcome in patients with solitary plasmacytoma of bone have been published. Additional information is now available on the role of serum free light chains and PET scanning. These recent publications are discussed below.

Epidemiological data continues to confirm a male: female ratio of 1.87 with median age of 60 years in patients with SBP (4). The axial skeleton especially the vertebrae remains the commonest site for SBP (4). SBP and myeloma are the commonest diagnoses in large reviews of primary bone tumours of spine (5).

The majority of patients with apparent SBP continue to develop myeloma. Up to 75% of patients at diagnosis may have a monoclonal protein in blood or urine, this is usually <10g/l (7). The rare cancer network published data on 206 patients with SBP, the largest series to date, in 2006 (6).

Despite treatment, 104 of 206 (50.4%) patients developed myeloma with a median time to development of 21 months (range, 2-135 months). 5 and 10 year projected probabilities of developing myeloma were 51% (95% CI, 43-59%) and 72% (95% CI, 62-82%). Age>60 years was the only independent predictor of development of myeloma in this study. Prognostic value of the persistence of a monoclonal band after treatment could not be assessed due to lack of data.

Multivariate analysis of prognostic factors in a series of 60 patients from the MD Anderson Hospital concluded that persistence of a monoclonal band for more than one year after radiotherapy was an adverse prognostic factor (7). In recent years an assay for serum free light chains (SFLC) has become available for clinical use and has transformed the monitoring of patients with non-secretory myeloma, light chain myeloma and amyloidosis. In patients with monoclonal gammopathy of undetermined significance (MGUS) an abnormal SFLC ratio appears to be an independent risk

factor for progression to myeloma (8). Dengli et al. retrospectively analysed stored serum of 116 patients taken at time of diagnosis of SBP between 1960 and 1995. An abnormal SFLC ratio was found in 54 (47%) patients and was associated with a higher risk of progression to myeloma ($p=0.039$) and an adverse overall survival ($p=0.033$) (9). Combining the results of the SFLC ratio at diagnosis with the serum monoclonal protein levels 1-2 years after diagnosis the researchers constructed a risk stratification model (Table 2) (9). Additionally, plasma cells with neoplastic phenotype demonstrable by flow cytometry at bone marrow sites distant to solitary plasmacytoma would also appear to predict for progression to myeloma (25). Genetic factors that have prognostic significance in myeloma such as del 13q and t(4;14) have, as yet, no proven value in solitary lesions.

Magnetic resonance (MR) imaging of the thoracic and lumbar spine was previously recommended for all patients diagnosed with SBP to exclude occult disease that may alter diagnosis to that of multiple solitary plasmacytomas or myeloma (1, 10). The new diagnostic criteria (Table 1) recommend MRI scanning to include the pelvis. Whole body MR imaging is emerging but currently impractical because of the logistics of long imaging time.

A prospective study by Schirrmester et al. assessed the accuracy of positron emission tomography (PET) scanning, which has the advantage of whole body imaging, in staging patients with presumed solitary plasmacytoma (11). Eleven of the 15 patients assessed had SBP, 4 had EP. Increased tracer uptake was seen in 9 of the 11 patients with bone lesions (sensitivity 86.7%). Additional lesions, not identified by standard staging methods, were found in 4 of the 11 patients altering therapy. PET is a potentially useful tool in the staging of such patients but cannot, as yet, be substituted for conventional imaging methods and currently remains an investigational tool rather than recommended for routine use (10, 11).

Diagnosis and investigation

SBP should be diagnosed by tissue biopsy. Fine needle aspirate is inadequate. Percutaneously guided biopsy of the spine is usually possible either by fluoroscopy or CT. All diagnoses should be made or reviewed by specialist haematopathologists in accordance with NICE guidelines for improving outcomes in haematological cancers (23). Monoclonality and /or an aberrant plasma cell phenotype should be demonstrated with useful markers being CD19, CD56, CD27, CD117 and cyclin D1 (24). IMWG diagnostic criteria are summarised in Table 1. The following investigations should be performed in all patients:

- full blood count
- biochemical screen including electrolytes and corrected calcium
- serum immunoglobulin levels
- serum and urine protein electrophoresis and immunofixation
- serum free light chain assay
- full skeletal survey, including standard x-rays of the skeleton including lateral and anteroposterior cervical, thoracic and lumbar spine, skull, chest, pelvis, humeri and femora*
- MRI of spine and pelvis (*or skeletal survey by MR where this facility exists)
- bone marrow aspirate and trephine

PET scanning may be useful in selected patients. Plasma cell phenotyping should be performed where available.

Treatment of SBP

Radical radiotherapy remains the treatment of choice for SBP (1). Knobel et al confirmed excellent local disease control with radiotherapy alone in their review of 206 patients with SBP (6). Local relapse occurred in 21(14%) out of 148 patients who received radiotherapy alone compared with 4(80%) out of 5 patients who were treated with surgery +/- chemotherapy. Surgery (radiotherapy

versus partial or complete resection and radiotherapy) did not influence the 10-year probability of local control. Median dose was 40Gy. No dose response relationship was observed for doses higher than 30Gy regardless of tumour size, however this was a retrospective analysis. Previous studies and BCSH recommend radical radiotherapy for SBP encompassing the tumour volume shown on MRI with a margin of at least 2cm and treating to a dose of 40Gy in 20 fractions with a higher dose of 50Gy in 25 fractions being considered for SBP>5cm (1). Surgery is not indicated for SBP, but some patients may require decompressive laminectomy, spine fusion or intramedullary rod fixation of a long bone.

There remains insufficient data to advice on adjuvant chemotherapy or the use of maintenance therapy such as Thalidomide in patients whose paraprotein persists following radiotherapy. Myeloablative therapy with stem cell support has been evaluated in a high-risk patients with SBP but numbers remain too small and follow up too short to draw any conclusions (12).

Recommendations

These remain unchanged from the previous guideline (1).

It is recommended that SBP is treated with radical radiotherapy, encompassing the tumour volume shown on MRI with a margin of at least 2cm and treating to a dose of 40 Gy in 20 fractions (grade B recommendation, based on level III evidence).

For SBP>5cm, a higher dose of up to 50 Gy in 25 fractions should be considered (grade C recommendation, based on level IV evidence).

Extramedullary plasmacytoma

Context

Extramedullary plasmacytomas (EP) are less common than SBP, occurring when there is soft tissue infiltration by clonal plasma cells. Over 80% of EP arise in the head and neck, especially the upper

respiratory tract with the gastrointestinal tract being the next most frequent site (1, 3). The tumours usually remain localised and progression to myeloma is uncommon. In contrast to SBP a monoclonal protein is detected in serum or urine in fewer than 25% of patients with EP (1).

Diagnosis and investigation

EP must be distinguished from reactive plasma cell lesions and lymphoma. It should be demonstrated that the infiltrate consists entirely of plasma cells and that there is no B cell component. In this regard CD138, MUM1/IRF4, CD20 and PAX5 are the most useful markers although it should be recognised that CD20 and PAX5 are sometimes expressed in plasma cell malignancies. Monoclonality and /or an aberrant plasma cell phenotype should be demonstrated with useful markers being CD19, CD56, CD27, CD117 and cyclin D1 (24,26). All diagnoses should be made or reviewed by specialist haematopathologists in accordance with NICE guidelines for improving outcomes in haematological cancers (23).

There have been no significant publications since the previous guideline on the role of SFLC or MR scanning in the diagnosis or prognosis of patients with EP. Additionally, because of the fewer numbers of patients, experience in the role of PET scanning for patients with EP is also scanty. Recommended investigations for all patients diagnosed with EP therefore remain unchanged from the previous guideline (1). IMWG diagnostic criteria for EP are summarised in Table 1.

Treatment of EP

Studies continue to show excellent local disease control and long-term disease free survival following radiotherapy. Since publication of the original guidelines three further studies have attempted to address the optimal radiotherapy dose and requirement for elective nodal irradiation. All are retrospective reviews. Tournier-Rangard et al. reviewed 17 patients treated between 1979 and 2003 (13). Five year local disease control was 90% for patients who received $\geq 40\text{Gy}$ compared

with 40% for those who received <40Gy (p=0.031). Patients who received \geq 45Gy had 100% local disease control but there was no statistical difference for local control for a patient who received a dose \geq 40Gy versus a dose \geq 45Gy (p=0.39). 5 year disease free survival was 64.1% overall. Five year survival rates for patients who received \geq 45Gy or < 45Gy were 87.5% and 37.5% respectively (p=0.056). Dose received to \geq 40Gy was not found to be a statistically significant prognostic factor for disease free survival. Approximately 25% of patients had progressed to myeloma at 5 years. Chao et al. identified 16 patients all of whom received radiotherapy with median dose 45Gy (range 40-50.4Gy) (14). Local control was achieved in all patients (100%). Michalaki et al. described 10 patients who received radiation doses of 40-50Gy with one local failure (10%) (15). This patient had previously received chemotherapy following an erroneous diagnosis of lymphoma. Median follow up for all patients was 29 months (range 7-67 months) with 70% overall survival. All the papers therefore continue to support radiation doses in the range 40-50Gy. Published data supports irradiation of involved lymph nodes but there remains inadequate data to make formal recommendations on elective irradiation of neck nodes. There have been no new studies on the role of surgery or adjuvant chemotherapy in patients with EP.

Whilst there is strong data for the efficacy of newer agents such as thalidomide and bortezomib in the management of patients with myeloma, evidence for their use in EP is based on case reports only. There has been one report, to date, of successful first line treatment of solitary extramedullary gastric plasmacytoma with the combination of bortezomib and dexamethasone, avoiding the potential toxicity of gastrointestinal irradiation (16). Additionally, bortezomib has been successfully used to debulk an extramedullary plasmacytoma involving ethmoid and maxillary sinuses before administering 40Gy radiotherapy (17). However, no recommendations can yet be made regarding the use of bortezomib in this setting.

Recommendations

These remain unchanged from the previous guideline (1).

Extramedullary plasmacytoma should be treated by radical radiotherapy encompassing the primary tumour with a margin of at least 2 cm (grade B recommendation, level III evidence). The cervical nodes should be included if involved. The first echelon cervical nodes should be included in EP of Waldeyer's ring (grade B recommendation, level III evidence). For EP up to 5cm a radiotherapy dose of 40 Gy in 20 fractions is recommended. For EP>5cm a higher dose of up to 50Gy in 25 fractions is recommended (grade B recommendation, level III evidence).

Multiple solitary plasmacytomas (+/-recurrent)

Context

Multiple solitary plasmacytomas, which may be recurrent, occur in up to 5% of patients with an apparently solitary plasmacytoma and may involve soft tissue or bone (2). By definition, there is no evidence of bone marrow involvement (Table I).

Treatment

Treatment approaches to patients with multiple solitary plasmacytomas (+/-recurrent) are variable and it is likely the choice of therapy will be influenced by factors such as patient age, sites of recurrence, numbers of lesions and disease free interval. Recurrent solitary plasmacytoma outwith the original site of radiotherapy, in the continuing absence of systemic disease, may be treated with additional radiotherapy. Patients with more extensive disease or early relapse may benefit from systemic therapy +/- autologous stem cell transplantation, as indicated for myeloma, with small cases series suggesting long term disease control (18, 19). Newer agents including thalidomide and bortezomib have also been used successfully, prior to transplantation, in small numbers of patients with relapsed plasmacytoma (20, 21, 22).

Recommendations

No clear recommendation for the treatment of multiple solitary plasmacytomas can yet be made.

Patient information and support

Provision of appropriate patient information and support remains a critical part of the care of patients with SBP and EP. Myeloma UK provide booklets and related resources for patients with solitary plasmacytoma and can be accessed at www.myeloma.org.uk.

Table 1. International Myeloma Working Group diagnostic criteria of solitary plasmacytoma of bone, extramedullary plasmacytoma and multiple solitary plasmacytomas (+/-recurrent)

DIAGNOSIS	CRITERIA
Solitary plasmacytoma of bone	No M-protein in serum and/or urine* Single area of bone destruction due to clonal plasma cells Bone marrow not consistent with multiple myeloma (plasma cells <5%) Normal skeletal survey (and MRI of spine and pelvis if done) No related organ or tissue impairment
Extramedullary plasmacytoma	No M-protein in serum and/or urine* Extramedullary tumour of clonal plasma cells Normal bone marrow Normal skeletal survey No related organ or tissue impairment
Multiple solitary plasmacytomas (+/- recurrent)	No M-protein in serum and/or urine* More than one localised area of bone destruction or extramedullary tumour of clonal plasma cells which may be recurrent

Variables	Risk group	5 year progression rate
Normal SFLC ratio Monoclonal protein <5g/l	Low	13%
Either variable abnormal	Intermediate	26%
Abnormal SFLC ratio Monoclonal protein >5g/l	High	62%
	Normal bone marrow Normal skeletal survey and MRI of spine and pelvis if done No related organ or tissue impairment	

*A small M-component may sometimes be present in blood or urine.

Table 2. Risk stratification model for SBP progression to myeloma using SFLC and monoclonal protein level

P<0.001

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