

LYMPHOID NEOPLASIA

Outcome prediction in plasmacytoma of bone: a risk model utilizing bone marrow flow cytometry and light-chain analysis

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Key Points

- Occult marrow disease is demonstrable in 68% of patients with solitary plasmacytoma of bone and is predictive of progression.
- Trials of adjuvant systemic therapy are warranted in high-risk patients.

The purpose of this study was to use multiparameter flow cytometry to detect occult marrow disease (OMD) in patients with solitary plasmacytoma of bone and assess its value in predicting outcome. Aberrant phenotype plasma cells were demonstrable in 34 of 50 (68%) patients and comprised a median of 0.52% of bone marrow leukocytes. With a median follow-up of 3.7 years, 28 of 50 patients have progressed with a median time to progression (TTP) of 18 months. Progression was documented in 72% of patients with OMD vs 12.5% without (median TTP, 26 months vs not reached; $P = .003$). Monoclonal urinary light chains (ULC) were similarly predictive of outcome because progression was documented in 91% vs 44% without (median TTP, 16 vs 82 months; $P < .001$). By using both parameters, it was possible to define patients with an excellent outcome (lacking both OMD and ULC, 7.7% progression) and high-risk patients (OMD and/or ULC, 75% progression; $P = .001$). Trials of systemic therapy are warranted in high-risk patients. (*Blood*. 2014;124(8):1296-1299)

Introduction

Solitary plasmacytoma of bone (SPB) is characterized by localized areas of bone destruction by monoclonal plasma cells in the absence of clinical, laboratory, and radiologic features of multiple myeloma (MM).¹ Local irradiation remains the treatment of choice. United Kingdom national guidelines recommend doses of 40 to 50 Gy depending on tumor size, with a 2-cm margin, because this provides excellent local control.² A significant proportion of patients will however progress with new lesions outside the irradiation field or, more typically, with generalized myeloma. The overall incidence of progression is 37% to 72%, with median reported times to progression (TTP) of 2 years or less.³⁻¹⁰

We hypothesized that progression in SPB might occur as a result of occult disease outside of the irradiation field. To further evaluate this, we used multiparameter flow cytometry (MFC) to assess staging bone marrow (BM) samples for the presence of occult disease and determine its impact on outcome.

Patients and methods

Fifty patients (median age, 65 years) with a histologically confirmed diagnosis of SPB according to International Myeloma Working Group (IMWG) criteria¹ were evaluated between 1998 and 2008. The solitary nature of the presenting lesion was confirmed by plain radiography in all patients, and 35 also had negative spinal magnetic resonance imaging results. Positron emission tomography (PET) scanning was not routinely performed. Thirty-five of 50 patients had a monoclonal protein (27 IgG, 7 IgA, and 1 light-chain

only) with a median concentration of 7 g/L. Urine immunofixation demonstrated monoclonal urinary light chains (ULC) in 11 of 45 patients, but the serum-free light-chain (SFLC) assay was not routinely available. Patients were treated in two regional radiation oncology centers with involved field irradiation with a median delivered dose of 41 Gy.

BM samples were obtained from sites distant from the presenting lesion (typically the iliac crest), and in each case, BM aspirate smears and trephine biopsies contained <5% plasma cells on morphologic assessment. MFC was performed in a single referral laboratory using previously published methods.¹¹⁻¹³ The gating approach used was in accordance with the European Myeloma Network (EMN) criteria¹⁴ in all cases: for identification of plasma cells, CD138, CD38, and CD45 expression with light scatter characteristics were assessed simultaneously in at least one tube. In cases analyzed with fewer than 6 fluorescence parameters, all tubes included at least 2 markers, usually CD38 and CD138, to identify plasma cells, with the optimal combination identified from the primary gating tube. According to the minimum criteria in the EMN consensus, the expression of CD19 and CD56 on gated plasma cells was analyzed in each case, with CD20, CD117, and CD27 also assessed in more recent cases. Occult marrow disease (OMD) was defined as a discrete population of phenotypically aberrant plasma cells comprising >30% of total BM plasma cells.

Disease progression was defined as the development of new solitary or multiple plasmacytoma (outside the irradiation field) or the development of symptomatic multiple myeloma as per IMWG criteria.¹ TTP and overall survival (OS) were determined from the time of initial diagnosis. Between-group comparisons were performed using the Fisher exact test, TTP and OS were assessed with Kaplan-Meier analyses and the log-rank test, and multivariate analysis was performed using Cox regression models. The study had institutional review board approval (Leeds Teaching Hospitals NHS Trust, Leeds, UK) and was conducted in accordance with the Declaration of Helsinki.

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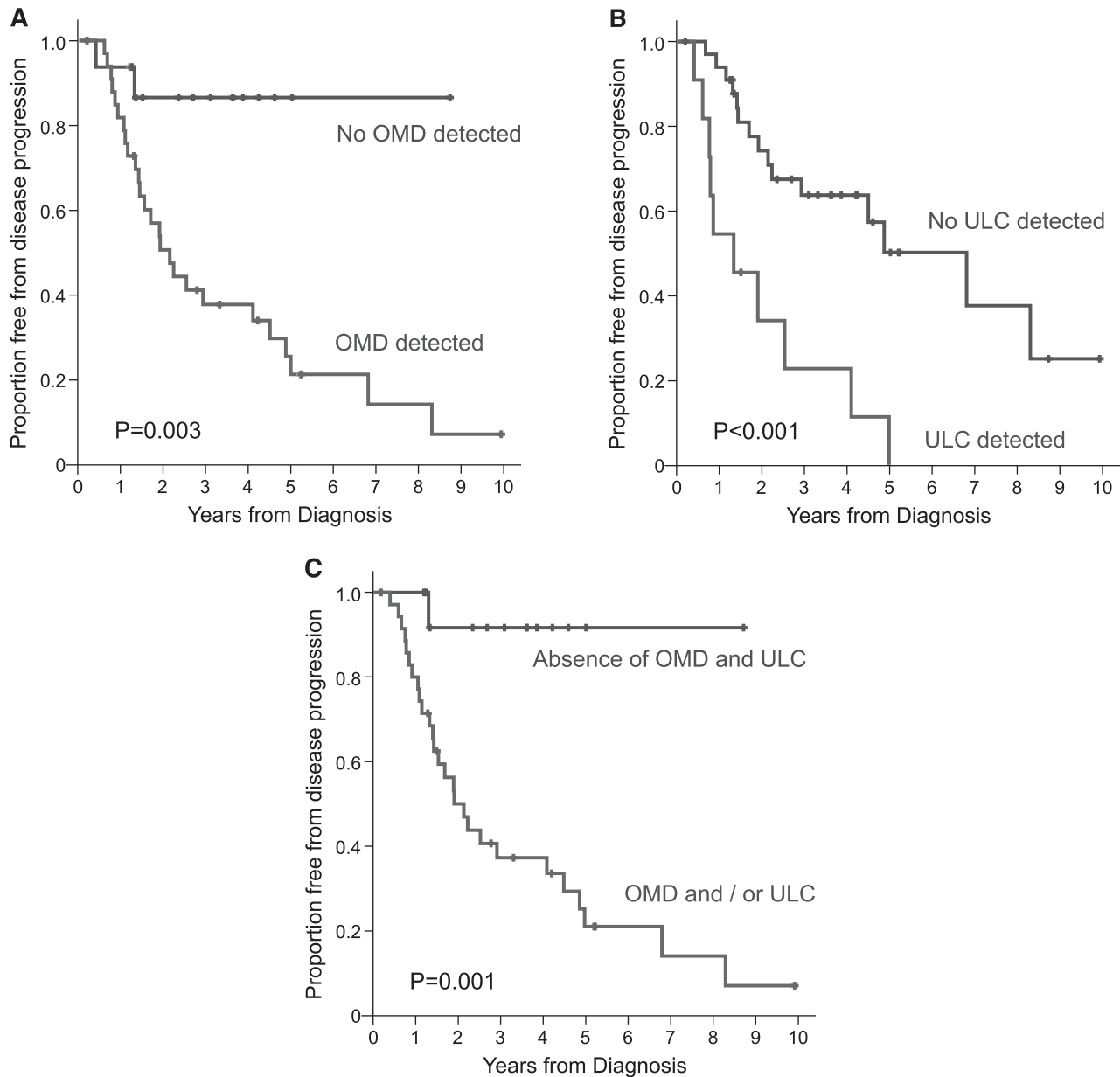


Figure 1. Progression in solitary plasmacytoma of bone: impact of occult marrow disease (OMD) and urinary light chains (ULC) on outcome. (A) OMD was demonstrable in 34 of 50 (68%) patients and was associated with an inferior outcome. Progression was documented in 72% (26/34) of patients with OMD compared with 12.5% (2/16) without. The median time to progression (TTP) was 26 months vs not reached, respectively ($P = .003$). (B) The presence of ULC was also associated with an inferior outcome because progression was documented in 91% (10/11) with ULC and 44% (15/34) without. The median TTP was 16 vs 82 months, respectively ($P < .001$). (C) When both parameters are assessed, patients may be defined as high risk by the presence of OMD and/or ULC (75% [24/32] progression), and they may be defined as low risk by the absence of both parameters (7.7% [1/13] progression). Median TTP was 23 months vs NR ($P = .001$).

Results and discussion

We hypothesized that OMD, distant from the primary lesion, would be demonstrable in patients with SPB and that this might influence progression. Aberrant phenotype plasma cells, indicative of OMD, were demonstrable in 34 of 50 (68%) patients and, when present, comprised a median 0.52% (0.03%-5.0%) of BM leukocytes and a median of 70% of BM plasma cells. With a median follow-up of 3.7 years, 28 of 50 (56%) patients have progressed, with myeloma developing in 22, new solitary lesions developing in five, and multiple plasmacytoma developing in one. The median TTP in this cohort was 49 months (18 months in those who progressed), and

this along with the overall proportion of patients progressing is broadly comparable with previous series.³⁻¹⁰ Progression was documented in 72% (26/34) of patients with OMD compared with 12.5% (2/16) without, and the median TTP was 26 months vs not reached (NR) ($P = .003$; Figure 1A). In a similar analysis, Warsame et al have demonstrated that the presence of clonal plasma cells (as determined by trephine biopsy immunohistochemistry), but below the 10% threshold for the diagnosis of myeloma, was associated with progression.¹⁰ Immunohistochemistry does, however, lack the sensitivity of MFC and will underestimate the proportion of patients with OMD.

The presence of ULC was also predictive of progression because it was documented in 91% (10/11) of patients with ULC vs 44% (15/34) without (median TTP, 16 vs 82 months, $P < .001$;

Table 1. Factors associated with progression in SPB

Factor	Univariate	Multivariate
Age	0.2	
Sex	0.44	
Vertebral location	0.31	
M protein at diagnosis	0.095	
Urinary light chains	<0.001	0.009
Occult marrow disease by MFC	0.003	0.041
Persistence of M protein at 1 year	0.07	

MFC, multiparameter flow cytometry.

Figure 1B). In contrast to previous studies,^{3-10,15} age, sex, vertebral location, or the presence of an M protein at diagnosis or its persistence at 1 year post-irradiation did not predict progression. The value of OMD and ULC were retained in multivariate analysis ($P = .041$ and $.009$, respectively; Table 1).

In developing a prognostic model for SPB, the main goal is the early identification of patients who have an excellent outcome after irradiation. Dimopoulos and colleagues reported that disappearance of the M protein at 1 year after irradiation predicted a favorable outcome.³ Likewise, Dingli and colleagues demonstrated the prognostic significance of an abnormal SFLC ratio as well as the persistence of the M protein at >1 year and proposed a prognostic model based on both parameters.⁴ The major limitation of these studies is the reliance on the 1-year M-protein assessment, and models providing for risk stratification at initial diagnosis are needed. Previous studies have consistently demonstrated the prognostic value of ULC and/or an abnormal SFLC ratio.^{3,4,10,16} We have confirmed these findings, but it is clear that a significant proportion of patients lacking ULC will progress. The absence of OMD, however, identifies a group of patients with an excellent outcome (12.5% progression, median TTP 26 months vs NR). This risk stratification may be further refined when outcome is assessed according to both OMD and ULC. For patients in whom both parameters were assessed, progression was documented in 75% (24/32) of patients with OMD and/or ULC but in only 7.7% (1/13) who lacked both parameters (median TTP, 23 months vs NR, $P = .001$; Figure 1C).

This model both stratifies at initial diagnosis and identifies patients who have an excellent outcome with irradiation. We would consider that a re-evaluation of the role of systemic therapy is warranted at this time. A small randomized trial has been performed in which 53 patients were randomized to either melphalan and prednisolone or to no further therapy after irradiation, and a benefit in TTP

and OS was demonstrated.¹⁷ This approach has not been further evaluated and, given the considerable therapeutic advances seen in myeloma, we would consider that a reevaluation of adjuvant therapy should be considered in high-risk SPB.

One of the limitations of this current analysis is the lack of PET imaging. Several studies have demonstrated that they are informative in SPB and upstage a proportion of patients.^{16,18-20} In a retrospective analysis, Warsame and colleagues suggested that the outcome in patients has improved since the introduction of routine PET imaging at their center because the outcome in patients with a negative PET scan was superior to those in whom PET was not performed.¹⁰ Similarly, Fouguet et al have recently demonstrated that additional lesions on PET imaging are associated with progression to MM.¹⁶ Further correlation of PET imaging, MFC, and SFLC is required because it is possible that truly solitary lesions will require a negative assessment with all modalities.

We would conclude that the presence of OMD, as demonstrated by MFC and ULC, are powerful predictors of progression in SPB, and trials of systemic therapy are warranted in high-risk patients.

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Authorship

Contribution: R.G.O. and A.C.R. conceived and designed the study; Q.A.H., A.C.R., and R.M.d.T. collected and assembled the data; all authors analyzed and interpreted the data; R.G.O. wrote the manuscript; and all authors gave final approval of the manuscript.

Conflict-of-interest disclosure: A.C.R. has a consultancy or advisory role with Celgene and BD Biosciences and received honoraria from Genzyme, GlaxoSmithKline, and Roche. R.G.O. has a consultancy or advisory role with Celgene and Pharmacyclics and received honoraria from Celgene and Janssen. The remaining authors declare no competing financial interests.

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