Multiple myeloma: causes and consequences of delay in diagnosis

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Summary

Background: Myeloma is a serious and usually fatal haematological malignancy with reported mortality of 10–20% within the first 2 months of presentation. Symptoms are non-specific, and patients thus present to a range of medical practitioners.

Aim: To analyse the causes and consequences of a delay in diagnosis of myeloma.

Design: Retrospective case review.

Methods: The number and type of disease-related complications present at diagnosis of 92 patients with myeloma were categorized according to the medical practitioner to whom the patient initially presented, the time before diagnosis and the status of the patient at study end in 2006. Overall and disease-free survival were analysed.

Results: Duration of symptoms >6 months prior to diagnosis was seen in 40% of the patients, of whom 50% had initially consulted a general practitioner. The most common presenting symptom (67%) was bone pain. The most common complications present at diagnosis were anaemia (54%), bone disease (45%) and renal failure (36%), with the highest frequency of complications in the group experiencing symptoms for >6 months. All patients in this group had two or more complications, while 40% in the group with symptoms for <3 months had no complications. A prolonged time to diagnosis had a significant effect on disease-free survival from both onset of first symptoms ($p=0.043$) and from diagnosis ($p=0.003$), but not on overall survival.

Discussion: A prolonged delay before diagnosis is associated with a significant impact on the clinical course of multiple myeloma. There is a need to raise awareness of the presentation of this condition, especially among general practitioners.

Introduction

Government initiatives have recently focused on reducing time to initiation of treatment for patients with malignant disorders. General practitioners (GPs) are urged to refer patients for urgent assessment, and hospital physicians are under pressure to assess and treat such patients within increasingly stringent time constraints. Two issues, however, have received insufficient attention. Firstly, earlier treatment, as opposed to earlier referral for specialist appraisal, does not equate to improved outcome for all malignancies. The commonest haematological malignancies in the developed world are the lymphoid malignancies, non-Hodgkin lymphoma, multiple myeloma and chronic lymphocytic leukaemia. Each of these conditions requires careful assessment prior to initiation of treatment, and many patients require follow-up, but not immediate treatment. Secondly, patients may present late, or elicitation of their symptoms may fail to lead to timely referral for specialist care. All doctors in...
primary and secondary care are aware of these issues, but few studies have systematically examined the consequences for patient outcome arising from delay in referral.

Multiple myeloma is one of the commonest haematological malignancies, with >4000 cases diagnosed annually in the UK. It is incurable, and the majority of patients diagnosed will ultimately die of it, although recent advances have raised patient expectations that better treatments may improve outcome. Patients with myeloma have three cardinal features at presentation.1 The most important is bone pain or pathological fractures arising from infiltration of the skeleton by malignant cells. All patients with myeloma who have skeletal involvement should commence treatment with chemotherapy, radiotherapy or both.2 The second is the presence of a paraprotein (an abnormal immunoglobulin produced by the malignant plasma cells) which is present in >95% of patients in either blood or urine or both.3 The third is the presence of an increased proportion (>10%) of plasma cells in the bone marrow. This can directly or indirectly lead to a decrease in normal marrow function, which can present as anaemia causing fatigue or as an increased susceptibility to infection. Other common complications of myeloma include renal failure, which can arise as a result of the toxicity of the filtered paraprotein to renal parenchymal cells, hypercalcaemia from the skeletal disease, infection or other complications including amyloidosis. We examined the causes and consequences of a delay in diagnosis among patients attending our myeloma clinic.

Methods

Hospital records of all patients attending the Royal Free Myeloma Clinic between 2001 and 2006 were reviewed. Patients presenting to a primary care physician (GP) with possible multiple myeloma may enter speciality care by a number of routes. The GP may refer the patient directly to haematology as suspected malignancy, whereupon he or she will be seen within a short time frame (under 2 weeks according to current targets). However if other symptoms, such as back pain or renal failure, are predominant, the patient may initially present (or be referred) to another speciality such as orthopaedics or nephrology. Data from referral letters from primary physician or other specialist, documentation from the initial patient consultation and pathology records were used to define the nature and timing of the first symptom experienced, and the time elapsing prior to a definitive diagnosis of myeloma. Wherever possible, contemporaneous source data rather than patient interview were used, to avoid the possibility of recall bias. The patients’ presenting symptom(s) recorded in the initial consultation with the haematologist, and the number and type of disease-related complications present at diagnosis, were analysed according to the time to diagnosis (0–3 months, 3–6 months, and >6 months), the medical practitioner to whom the patient initially presented, and the present status of the patient. Disease-free and overall survival for each group were compared by Kaplan-Meier analysis (Graphpad Prism 4). All patients were treated according to guidelines adopted by the North London Cancer Network, based on national recommendations.2,5

Illustrative case

A 76-year-old male presented to his primary care physician with back pain in August 2002. He was treated with analgesia, with good relief, and on subsequently being found anaemic was also prescribed haematin supplementation. In December 2003, he presented with urinary tract symptoms. Serum protein electrophoresis detected a monoclonal protein, and he was referred to a haematologist, who confirmed the diagnosis of myeloma. His presenting symptom was therefore bone pain, the time to diagnosis was 16 months, and the complications at diagnosis were radiologically-confirmed bone disease, renal failure and anaemia.

Results

Characteristics of patients

In total, 103 patients attended the Royal Free Myeloma Clinic between 2001 and 2006. Sixty were male, with a median age of 67 years (range 50–86 years) and 43 were females, median age 63 years (range 26–84 years). Ninety-two were diagnosed as de novo myeloma patients, while eleven patients were being followed up in the clinic with smouldering myeloma (two), monoclonal gammopathy of undetermined significance (six) or plasmacytoma (three) and developed overt myeloma while under follow-up. These eleven patients were excluded from further analysis, as there is effectively zero time to referral for patients already attending the haematology clinic. Eleven of the 92 patients died during the study period.

Delay in diagnosis

Twenty-eight of the 92 patients were diagnosed within a period of 3 months of the first symptom. For the remaining 64 (70%), >3 months elapsed
between the onset of the first symptom and the diagnosis of myeloma (Table 1). Twenty-six of 54 males (48%) and 17/38 females (44%) were diagnosed after 6 months after their first symptom. The most frequent disease-related complications seen in our patients were bone disease, renal impairment, infection, neurological complications, and anaemia. The median number of complications in males was two, compared to one in females.

**Initial presentation**

The practitioner to whom the patient first presented, and the interval between the first symptom and the diagnosis, are listed in Table 1. Fifty-one patients (55%) initially presented to a general practitioner, and for 56% of these there was an interval of >6 months (>12 months in 33%) before specialist referral. Three patients presented to a haematologist, two for anaemia and one for a thrombotic disorder. All these patients were diagnosed within 3 months of the first symptom. Overall, a delay of >6 months between first symptom and definitive diagnosis was seen in 43 patients, 29 (67.4%) of them initially presenting to a general practitioner. Five of the 29 (17%) delayed their own presentation to the GP, whereas 23 (79%) visited a GP within 2 weeks of the onset of symptoms. The increased time to diagnosis was therefore principally due to increased time to specialist referral. In those instances where patients had initially presented to a GP who had then referred the patient to a relevant physician, the delay was recorded on the part of the specialist physician.

**Presenting symptoms**

The presenting symptoms of the 92 de novo myeloma patients are listed in Figure 1. Bone pain was the most frequent symptom in this cohort (67%).

### Table 1 Interval before diagnosis, according to the presenting physician

<table>
<thead>
<tr>
<th>Interval (months), All</th>
<th>0–3</th>
<th>3–6</th>
<th>&gt;6</th>
</tr>
</thead>
<tbody>
<tr>
<td>GP</td>
<td>51</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Haematologist</td>
<td>3</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Rheumatologist</td>
<td>4</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Nephrologist</td>
<td>6</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Neurologist</td>
<td>3</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Orthopaedic</td>
<td>4</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>A&amp;E</td>
<td>8</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Homeopath</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Oncologist</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>ENT</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Physicist</td>
<td>8</td>
<td>4</td>
<td>3</td>
</tr>
</tbody>
</table>

The second commonest was a global feeling of ill-health (‘asthenia’), in 14%.

**Complications at diagnosis**

The clinical complications detected in these patients (as opposed to the reported symptoms), and the interval between the first symptom and diagnosis, are shown in Figure 2, a and b. Eighteen patients had no complications, vs. 74 who did. The most frequent complications were anaemia (50/92, 54%) followed by bone disease (42/92, 45%) and renal impairment (34/92, 36%). Of the 51 who initially presented to a general practitioner, 45 (88%) had complications at diagnosis. When stratified according to Durie-Salmon stage at diagnosis (Table 2), 45.5% of those diagnosed within
3 months presented at stage I and 7% at stage III, compared to 16% and 28.5%, respectively, of those patients diagnosed at >6 months (\(p=0.04\), \(\chi^2\)).

Table 3 shows the status of the patients at the end of the study period, related to the interval between the first symptom and diagnosis. Patients who had undergone allogeneic transplantation were excluded, as morbidity and mortality are significantly affected by the transplant procedure. Twenty-two (78%) of the patients in group with <3 months symptoms before diagnosis were either in the first phase of remission induction or in a stable phase, 4 (14%) had relapsed disease and two (7%) were dead. By contrast, 22/41 (51%) evaluable patients in the group with >6 months to diagnosis were either in the first phase of remission induction or in a stable phase, 6 were dead (14%) and 13 (30%) were in the relapsed phase of the disease (\(p>0.05\), \(\chi^2\)). Eleven patients died during the duration of the study, of whom six had an initial time to diagnosis of >6 months.

**Effect of delay in diagnosis on survival**

It could be argued that earlier diagnosis might not benefit overall survival, and instead only lengthens the duration of time that the patient survives with knowledge of the diagnosis. We therefore used Kaplan-Meier analysis to compare overall and disease-free survival both from the time of diagnosis and also from the original onset of symptoms (Figure 3). The log rank test revealed a significant
impact of delayed diagnosis on disease-free survival not only from diagnosis \((p = 0.003)\), but also from original symptom onset \((p = 0.043)\). No significant effect on overall survival was demonstrated.

**Discussion**

Multiple myeloma is not a rare condition; some 4000 patients present each year to secondary care. With a mean survival from diagnosis of 4–5 years, there are between 20000 and 30000 multiple myeloma patients at any time in the UK. The presenting features of multiple myeloma are non-specific. Anaemia is seen in 40% of patients with symptomatic myeloma. Up to 70% have skeletal disease, which causes pain, reduces mobility and may result in hypercalcaemia.\(^1\) Renal impairment is present in up to 30% at diagnosis.\(^1\) An analysis of patients entered onto the UK Medical Research Council trials for myeloma between 1980 and 2002 reported that of a total of over 3000 newly diagnosed myeloma patients, 299 (10%) died within 60 days of trial entry.\(^6\) Performance status and age were poor predictors of early mortality. ‘Delay in presenting to medical care’ was reported to be associated with early mortality, but no detailed information is available in the trial reports. Indeed, there are very few data on the causes, circumstances and consequences of delay in diagnosis of multiple myeloma.

We were prompted to undertake a comprehensive review of the patients attending our myeloma clinic following our frequent observation that patients reported a delay between reporting their first symptom and being referred for assessment. Government initiatives have focussed increasingly on reducing the delay between referral by general practitioners and hospital attendance. A further delay is perceived to occur between hospital attendance and institution of tests leading to diagnosis; with further delay occurring before actual commencement of therapy. Most of these delays are due to structural problems within the Health Service. Our perception from working within the myeloma clinic, however, was that significant delays were occurring between the date at which patients first noticed the symptom with which they presented to their primary physician; and then a subsequent time before institution of appropriate investigation and referral.

Reducing the delay between first symptom and diagnosis of myeloma is not straightforward, and the delay should not be seen as a failure of primary care. Many of the symptoms are non-specific, and immediate referral of all patients with back pain, for example, is not practical or indicated. A comprehensive review of the diagnosis and treatment of lower back pain indicates conditions that should alert the primary care physician to the possibility of underlying spinal pathology (age of onset <20 or >55 years, pain unrelated to activity, thoracic pain, previous history of carcinoma, steroids or HIV, feeling generally unwell with anorexia, weight loss, structural spinal deformity)\(^7\). A study from the US found that of all patients with back pain in primary care, <1% had a tumour or metastasis.\(^8\) A study from a secondary care centre in Denmark however, reported that 18/366 patients (5%) with osteoporosis had a monoclonal paraprotein band or overt multiple myeloma.\(^9\) Literature directed at general practitioners has aimed to raise awareness of myeloma and associated conditions.\(^4\)

In our study, a significant delay in diagnosis (>6 months) occurred in >40% of patients. Increased time from first symptom to diagnosis commonly occurred in those patients whose initial consultation was with a general practitioner. Delay was more common in males than females, and males tended to have more complications at presentation. Patients who had a delay of ≥6 months were more likely to have an increased number of complications, Durie-Salmon stage III and reduced disease-free survival, measured both from onset of symptoms and from time of diagnosis. The effect of prolonged time to diagnosis on disease-free survival from the onset of the original symptoms implies an impact on the durability of remissions achieved after a delay in initial diagnosis and commencement of treatment. Our data do not show a significant difference in overall survival, but there was a trend to reduced overall survival from diagnosis in the group with the longest delay.

### Table 3 Patient status at study end, according to time from first symptom to definitive diagnosis of myeloma

<table>
<thead>
<tr>
<th>Delay in diagnosis (months)</th>
<th>Induction</th>
<th>Stable disease</th>
<th>Relapse</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–3</td>
<td>10 (35.7%)</td>
<td>12 (42.8%)</td>
<td>4 (14.2%)</td>
<td>2 (7.1%)</td>
</tr>
<tr>
<td>3–6</td>
<td>4 (19%)</td>
<td>10 (47.6%)</td>
<td>4 (19.4%)</td>
<td>3 (14.2%)</td>
</tr>
<tr>
<td>&gt;6</td>
<td>14 (34.1%)</td>
<td>8 (19.5%)</td>
<td>13 (31.7%)</td>
<td>6 (14.6%)</td>
</tr>
</tbody>
</table>

Data are numbers (% patients in that diagnostic category).
This finding should be confirmed in a larger cohort of patients with longer follow-up and co-analysis of other biological factors.

We feel that there is a critical need to increase awareness of myeloma and related conditions within medical communities and the general public in the UK. The incidence of myeloma seems to be increasing worldwide. We are planning to undertake a larger study of myeloma patients in the UK through the patient support organization Myeloma UK [www.myeloma.org.uk].

References