Impact of Initial FDG-PET/CT and Serum-Free Light Chain on Transformation of Conventionally Defined Solitary Plasmacytoma to Multiple Myeloma

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Abstract

**Purpose:** Solitary plasmacytoma (SP) is a localized proliferation of monoclonal plasma cells in either bone or soft tissue, without evidence of multiple myeloma (MM), and whose prognosis is marked by a high risk of transformation to MM.

**Experimental Design:** We studied the impact of FDG-PET/CT (2[18F]fluoro-2-deoxy-D-glucose positron emission tomography–computed tomography) on the risk of transformation of SP to overt MM among other markers in a series of 43 patients diagnosed with SP.

**Results:** Median age was 57.5 years; 48% of patients had an abnormal involved serum-free light chain (sFLC) value, and 64% had an abnormal sFLC ratio at diagnosis. Thirty-three percent had two or more hypermetabolic lesions on initial PET/CT, and 20% had two or more focal lesions on initial MRI. With a median follow-up of 50 months, 14 patients transformed to MM with a median time (TTMM) of 71 months. The risk factors that significantly shortened TTMM at diagnosis were two or more hypermetabolic lesions on PET/CT, abnormal sFLC ratio and involved sFLC, and to a lesser extent at completion of treatment, absence of normalized involved sFLC and PET/CT or MRI. In a multivariate analysis, abnormal initial involved sFLC [OR = 10; 95% confidence interval (CI), 1–87; P = 0.008] and PET/CT (OR = 5; 95% CI, 0–9; P = 0.032) independently shortened TTMM.

**Conclusions:** An abnormal involved sFLC value and the presence of at least two hypermetabolic lesions on PET/CT at diagnosis of SP were the two predictors of early evolution to myeloma in our series. This data analysis will need confirmation in a larger study, and the study of these two risk factors may lead to a different management of patients with SP in the future. *Clin Cancer Res;* 1–7. ©2014 AACR.

Introduction

Solitary plasmacytoma (SP) is a rare plasma cell neoplasia characterized by a localized proliferation of monoclonal plasma cells resulting in a tumor, without evidence of either bone marrow plasma-cell infiltration or systemic plasma-cell proliferative disorder, for example, absence of evidence of multiple myeloma (MM; refs. 1–4). SP can be localized in either bone (solitary bone plasmacytoma; SBP) or soft tissue [extramedullary plasmacytoma (EMP), usually located on the head and neck, and especially in the nasal cavity and nasopharynx; ref. 1]. Multiple SP can be observed in up to 5% of patients. The prognosis of SP is essentially marked by a high risk of transformation to MM, which occurs in almost 50% of patients with SBP (4), 15% of patients with EMP (5), and can happen up to 15 years after diagnosis. Historical prognosis factors for progression to MM are SBP (compared with EMP), older age, tumor size > 5 cm (6), and persistence of monoclonal immunoglobulin at completion of treatment (7).

The presence of focal lesions on MRI is an important prognostic factor in MM (8), particularly in smoldering multiple myeloma (SMM; ref. 9), including those with plasmacytoma (10). Recent studies showed that FDG-PET/CT (2[18F]fluoro-2-deoxy-D-glucose positron emission tomography–computed tomography) provides additional valuable information for the assessment of MM compared with Magnetic Resonance Imaging (MRI) (11), especially in the presence of plasmacytoma (12, 13). The prognostic role of PET/CT has not been formally determined in SP, nor has its role been studied in reassessment of diagnosis from SP to multiple SP.

We aimed to determine the impact of FDG-PET/CT in the management of SP for the evaluation of the risk of progression to MM.
Materials and Methods

Patients

We retrospectively reviewed the medical records of 43 patients from three French centers (Lille, Caen, and Rennes) of the IFM (Intergroupe Francophone du Myelome), diagnosed from 2002 to 2013 with an SP.

All patients had clinical evidence of a SP, either EMP (10 patients) or SBP (33 patients). The diagnosis of plasmacytoma was confirmed by histologic evidence of a tumor made of a proliferation of monoclonal plasma cells, as described in guidelines. The initial evaluation of SP ensured the absence of criteria for MM, especially a bone marrow not consistent with MM (<10% plasma cells) and no end organ damage or tissue impairment defined by the absence of the CRAB criteria (hypercalcemia, renal insufficiency, anemia, or bone lesions using standard whole body X-rays other than solitary bone lesion in the case of SBP; ref. 4). Treatment of SP consisted in surgery when possible (especially for EMP) and/or radiotherapy, from 30 to 50 Grays in our study.

The study was approved by the ethics committee of CHRU of Lille, France and was conducted in accordance with the principles of the Declaration of Helsinki.

Assessment

Whole body PET/CT and MRI of the spine and pelvis were performed at diagnosis before (initial) and at completion of therapy (3 months to 1 year after the end of treatment). Serum-free light chains (sFLC) were assessed by the value of involved sFLC (isFLC) and by the \( k/\lambda \) ratio (abnormal if \( <0.26 \) or \( >1.65 \)). All patients had complete follow-up records before and after therapy. When hypermetabolic lesions were identified on PET/CT, standard X-rays were always performed if possible; however, we have relied on the CT part of the PET/CT most of the time to identify the presence or absence of underlying osteolytic bone lesions.

Statistical analysis

Descriptive data were collected for the cohort. All survival endpoints were evaluated through the Kaplan–Meier estimates and compared through the log-rank test. The relative risk of event and its 95% confidence interval (95% CI) were estimated through proportional hazard model. Univariate and multivariate analysis were performed. We constructed a four categories model based on two variables, isFLC and PET/CT at diagnosis, the two independent variables that affected TTMM using multivariate analysis. The categories that did not show any statistical difference for the study of the TTMM endpoint were regrouped, that is to say, the two categories characterized with either “at least two hypermetabolic lesions on PET/CT” or “abnormal involved sFLC” were regrouped. The subsequent prognostic model was thus simplified to a final model with three categories. All analyses were done with the SPSS 15.0 software.

Results

Characteristics of patients

Table 1 summarizes the characteristics of the patients. The median age was 57.5 years, with 33% patients older
than 65 years. The sex ratio was 1.8. Eighteen (42%), 21 (49%), 11 (26%), and 24 (56%) patients had a measurable disease, using serum protein electrophoresis (SPEP; serum and/or urine), isFLC, sFLC ratio, and immunofixation (serum and/or urine), respectively. Immunoglobulin G (IgG)-κ was the most frequent isotype, and the higher M-spike value was 30 g/L. Although all studied patients had a unique clinical evidence of SP, we noticed that 10 (23%) had at least two hypermetabolic lesions on initial PET/CT, and 7 (16%) had at least two focal lesions on initial MRI. The median number of either hypermetabolic lesions or focal lesions on the initial PET/CT or MRI, respectively, was 2 (median 1, range minimum–maximum 1–3). The other hypermetabolic lesions or focal lesions did not correspond to osteolytic lesion or any other soft tumor mass, as assessed by standard X-rays and by the CT part of the TEP/CT. Out of the SBP, 17 (51%) were localized on spine or pelvis.

Fifteen patients (34.8%) developed a MM in our series and 5 patients (11.6%) died during follow-up. Amongst the 10 patients with at least two hypermetabolic lesions on initial PET/CT, 6 patients progressed to MM. Similarly, amongst the 7 patients with at least two focal lesions on MRI at diagnosis, 4 patients progressed to MM. Fifteen patients had an abnormal isFLC at diagnosis, amongst whom 9 patients developed a MM.

Shorter TTMM correlated with initial PET/CT and isFLC value

With a median follow-up of 50 months, the median time to MM progression (TTMM) was 71 months for the whole cohort (95% CI, 59–101). We found no significant difference of TTMM between SBP and EMP, although the 5-year TTMM was 45% and 83%, respectively (Table 2).

Using univariate analysis, we found that sFLC but not SPEP M-spike or immunofixation, and PET/CT but not MRI, influenced TTMM (Table 2). The TTMM for the group with at least two hypermetabolic lesions on initial PET/CT was 23 months (9–37) versus not reached otherwise ($P = 0.003$; Fig. 1A). Conversely, MRI at diagnosis did not have any impact on TTMM in our study, although the median TTMM for the group with at least two focal lesions on initial MRI was lower, 30 months (9–51) versus not reached otherwise ($P = ns$). We also observed that abnormal initial $k/l$ ratio ($P = 0.022$) and abnormal initial isFLC value ($P = 0.002$) did impact TTMM, 36 (14–58) and 21 months (0–42) versus not reached otherwise, respectively (Fig. 1B).

Surprisingly, a normalized PET/CT (defined by the absence of remaining hypermetabolic lesion on the main plasmacytoma that required therapy) at completion of treatment did not reach significance, as to a normalized MRI (similar definition), but the absence of a normalized isFLC value also impacted TTMM, 21 months (10–32) versus not reached otherwise ($P = 0.016$).

Using multivariate analysis, initial isFLC value (OR = 10; 95% CI, 1–87; $P = 0.008$) and initial PET/CT (OR = 5; 95% CI, 0–9; $P = 0.032$) were the strongest independent prognostic factors that impacted TTMM. On the basis of these results, we proposed a model of four categories with these two variables. The most adverse categories about TTMM included patients with abnormal initial isFLC value and at least two hypermetabolic lesions on initial PET/CT (PET $\geq$ 2; with all but one patient that developed overt MM), whereas the group with normal initial isFLC value and < 2 hypermetabolic lesions on initial PET/CT (PET < 2) displayed the best prognostic (with none of the patients that developed overt MM). The remaining two categories with abnormal initial isFLC and PET $<$ 2 or with normal initial isFLC and PET $\geq$ 2 had an intermediate prognostic, with no statistical significant difference between the two groups. We thus regrouped these two categories to create a simplified three categories with two variables model. Using this latter model, we have been able to separate the three groups with median ($\pm$SE) TTMM of 21 ($\pm$2) months for the worse category (5 patients, including 4 (80%) that developed MM), 41 ($\pm$2) months for the intermediate category (24 patients, amongst whom 11 patients (45.8%) developed a MM), and finally median TTMM not reached for the best category (14 patients, none developed a MM; $P = 0.004$ and 0.002, respectively; Table 3; Fig. 1C).

### Table 2. Impact of biologic test and medical imaging factors on TTMM progression ($N = 43$)

<table>
<thead>
<tr>
<th>Category</th>
<th>Median TTMM (CI 95%)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>At diagnosis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Localization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SPB</td>
<td>23 months (25–116)</td>
<td>ns</td>
</tr>
<tr>
<td>EMP</td>
<td>Not reached –</td>
<td></td>
</tr>
<tr>
<td>PET/CT (hypermetabolic lesions)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$&lt;$ 2</td>
<td>Not reached –</td>
<td></td>
</tr>
<tr>
<td>$\geq$ 2</td>
<td>23 months (9–37)</td>
<td>0.003</td>
</tr>
<tr>
<td>MRI (focal lesions)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$&lt;$ 2</td>
<td>Not reached –</td>
<td></td>
</tr>
<tr>
<td>$\geq$ 2</td>
<td>30 months (9–51)</td>
<td>ns</td>
</tr>
<tr>
<td>isFLC value</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>Not reached –</td>
<td></td>
</tr>
<tr>
<td>Abnormal</td>
<td>21 months (0–42)</td>
<td>0.002</td>
</tr>
<tr>
<td>$k/l$ ratio</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>Not reached –</td>
<td></td>
</tr>
<tr>
<td>Abnormal</td>
<td>36 months (14–58)</td>
<td>0.022</td>
</tr>
<tr>
<td><strong>At completion of treatment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PET/CT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normalized</td>
<td>Not reached –</td>
<td></td>
</tr>
<tr>
<td>Not normalized</td>
<td>60 months (25–95)</td>
<td>ns</td>
</tr>
<tr>
<td>MRI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normalized</td>
<td>Not reached –</td>
<td></td>
</tr>
<tr>
<td>Not normalized</td>
<td>Not reached –</td>
<td></td>
</tr>
<tr>
<td>isFLC value</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normalized</td>
<td>Not reached –</td>
<td></td>
</tr>
<tr>
<td>Not normalized</td>
<td>21 months (10–32)</td>
<td>0.016</td>
</tr>
</tbody>
</table>

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**Note:** $P$-values are given for the univariate analysis.
With a special focus on SBP, we identified the exact same prognostic factors for TTMM as for the whole cohort, in univariate and multivariate analysis. The localization of SBP in the spine is usually considered of poor prognosis, but we did not find any confirmation of this observation in our study.

Figure 1. Time to progression toward MM according to isFLC and PET/CT at diagnosis of SP. A, on the basis of ≥2 hypermetabolic lesions on initial PET/CT versus <2 lesions. B, on the basis of normal versus abnormal isFLC value. C, risk model with two variables and three categories (Table 3): 1, the group with normal isFLC and <2 hypermetabolic lesions on initial PET/CT; 2, the group with either abnormal isFLC value and <2 hypermetabolic lesions on initial PET/CT or normal isFLC value and ≥2 hypermetabolic lesions on initial PET/CT; 3, the group of patients with abnormal initial isFLC value and ≥2 hypermetabolic lesions on initial PET/CT.

Table 3. Proposed risk model for progression from SP to MM, with two variables and three categories

<table>
<thead>
<tr>
<th>Categories</th>
<th>TTMM Median, mo (± se)</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Normal isFLC + PET/CT &lt; 2</td>
<td>NR</td>
<td>—</td>
</tr>
<tr>
<td>2</td>
<td>Abnormal isFLC + PET/CT &lt; 2 or normal isFLC + PET/CT ≥ 2</td>
<td>41 (2)</td>
<td>5 (0–16)</td>
</tr>
<tr>
<td>3</td>
<td>Abnormal isFLC + PET/CT ≥ 2</td>
<td>21 (2)</td>
<td>25 (0–76)</td>
</tr>
</tbody>
</table>

NOTE: 1, represents the group with normal isFLC and <2 hypermetabolic lesions on initial PET/CT; 2, represents the group with either abnormal isFLC value and <2 hypermetabolic lesions on initial PET/CT or normal isFLC value and ≥2 hypermetabolic lesions on initial PET/CT; and 3, represents the group of patients with abnormal initial isFLC value and ≥2 hypermetabolic lesions on initial PET/CT. Abbreviations: se, standard event; HR, relative risk of event; P, significance.
Shorter TTMM is not associated with shorter OS in our series

The median overall survival (OS) was not reached for the whole cohort, with a 6-year OS at 79.4%. Although the median OS of patients with SP from start of MM was not reached, similar to SP that did not progress toward MM, the 4-year OS was 66% compared with 92% (P = ns). This difference did not appear statistically shorter, but that might be related to the limited number of patients recruited in the study. Interestingly, initial PET/CT did not seem to influence OS, with a median of 71 months for the "PET ≥ 2" group versus not reached otherwise, respectively (P = ns). Similar observation was obtained with isFLC value.

The presence of SP at the time of MM diagnosis is usually considered adverse prognostic for OS. Interestingly, when considering the prolonged OS of patients with SP that transformed later on to MM, and compared with de novo MM in the literature, we could extrapolate that SP that transformed to MM were not of worst prognostic compared with newly diagnosed myeloma with no features of adverse prognostic. It seems that the SP that transformed toward MM could appropriately be rescued by the current therapeutic approach of myeloma.

Discussion

Because the major issue in the management of SP lies in its inherent risk of transformation to MM, initial assessment should be focused on the detection of asymptomatic lesions to ensure that the patient does not already have a widespread disease that would require a systemic treatment or, more importantly, an occult lesion from which MM would develop and spread over the whole body bone marrow. Biologic factors at diagnosis of SP have been associated to the risk of development of MM, mainly markers of the M-spike component as an assessment of the initial tumor burden. There has always been a great need for iconography to identify these occult lesions, and the introduction of MRI was an important breakthrough compared with the historical use of skeletal X-rays, CT scanner and scintigraphy; however, the question of the best imaging technique for the detection of these occult lesions is not yet fully resolved.

In this study, we found that the presence of at least two hypermetabolic lesions detected by FDG-PET/CT was an important risk factor for progression to MM, compared with none or only one hypermetabolic lesion. This suggests that the diagnosis of SP should not be solely based on clinic, but should integrate sensitive imagery techniques. We believe, although we acknowledge that it is a matter of debate still, that PET/CT is one of them, possibly similar to whole body MRI. This could imply that patients with multiple pathologic lesions, even if no proof of a widespread disease is found, could already present an early stage of MM and be at risk of transformation when treated only locally. In that setting, the identification of multiple hypermetabolic signals, even though not clinically relevant in the context of SP, should modify the diagnosis to multiple SP and thus make consider systemic treatment as to MM treatment approach (14).

PET/CT was rarely investigated in SMM and SP, and seemed to be a very promising technique, but its value is not well recognized yet (15). Warsame and colleagues found that the association of a negative PET/CT and a negative bone marrow (but not a negative PET/CT alone) had a good predictive value for a lower likelihood of progression to MM, in a retrospective series of 127 SBP at Mayo Clinic (Rochester, MN; ref. 16); an abnormal initial k/λ ratio was also a poor prognostic factor for progression to MM. Kim and colleagues confirmed FDG-PET/CT as a useful technique for initial staging of SP, and also for response assessment after radiotherapy (17). These findings are consistent with those found in related plasma cell diseases, such as monoclonal gammopathy of undetermined significance (MGUS) and SMM. Durie and colleagues also showed that the presence of extramedullary hypermetabolic lesions on PET/CT was a poor prognostic factor either at start of treatment or at relapse, in a series of 66 patients with MM at different stages of the disease (18). Furthermore, a persistent abnormal FDG uptake after treatment was predictive of relapse.

The impact of MRI was not significant in our series, but patients with at least two focal lesions seemed to be at higher risk of progression than the others. Few studies have shown that abnormal MRI can impact the progression to MM for SMM (9) and SP (10). MRI was thus considered a major imagery technique for the initial staging of SP, able to detect asymptomatic lesions that would orientate the diagnosis towards MM with presence of plasmacytoma rather than SP (10).

Recent studies have found that FDG-PET/CT provides additional valuable information for the assessment of MM compared with MRI (11). Salaun and colleagues compared the value of MRI and FDG-PET/CT for SP in a series of 24 patients at diagnosis for initial staging and after treatment (12). They found that PET is equivalent to MRI for evaluation of spine and pelvis, but that it allowed a better evaluation of soft tissues, skull, ribs, and limbs. They also concluded that PET/CT showed a higher performance than MRI for therapeutic assessment.

Oddly, the correction of PET/CT lesions after treatment (defined by the absence of remaining hypermetabolic lesion on the main plasmacytoma that required therapy) was not significantly associated with a longer TTMM, neither did the correction of MRI lesions. However, as there is a lack of recommendations for the use of PET/CT in SP, the ideal time for posttreatment assessment is not defined and several patients had a PET/CT quickly after treatment in our study. The persistence of abnormal FDG uptake could have been distorted by recent treatments, especially after radiotherapy.

Interestingly, in our series, the presence of at least two hypermetabolic lesions detected by PET/CT impacted the TTMM progression, but not the OS. Although our data seem to say that patients who developed MM later on after diagnosis of SP did not seem to have a poorer prognostic at time of MM than patients with de novo MM with no adverse features in the same age group, the 4-year OS was
shorter in these patients compared with SP that did not progress to MM. These data should be confirmed in a larger study.

The concerns over identifying and treating plasma cell malignancies earlier in the malignant process development have never been as present as nowadays, with the recent understanding that clonal evolution occurs very early in malignant plasma cells. One would hope that early treatment of SP could give the patient a chance to cure, while this cure cannot be obtained after progression to MM, as it is considered a very complex genomic cancer at the time of transformation (19).

The identification of subgroups of SMM and SP with a greater risk to develop overt MM (possibly renamed as early MM in the near future, at least for the high-risk SMM) in a short period of time is of importance and relevance to the field and to the patients. A study recently demonstrated that high-risk SMM seemed to highly benefit from early treatment approach in terms of prolonged TTMM and more importantly OS, rather than to wait for development of symptomatic MM to start treatment (20). The definition of early MM remains debatable, and whether all currently defined high-risk SMMs are early MM, remains however an important matter of debate (21). Similarly, an early treatment for SP should only be proposed to patients identified as being at higher risk, through well-defined prognostic risk factors. It must be proven at least equivalent to local treatment in terms of response, and superior with regard to PFS, or even OS. Finally, it must have an acceptable toxicity profile to avoid side effects related to a possibly unnecessary treatment, and preserve the patient’s quality of life. FDG-PET/CT and isFLC values are important predictors of the risk of progression from SP to MM in our study. PET/CT seems to be a sensitive technique to help reveal multiple hypermetabolic lesions, beyond the clinical SP presentation, that should encourage experts to revise the diagnosis of SP and possibly rename this as multiple SP—corresponding to early myeloma because early systemic MM treatment approach is recommended (14).

This data analysis may lead to a different management of SP for patients with one or both of these two abnormal indicators, irrespective to the solitary clinical aspect of SP. One may consider to embrace systemic treatment (that is to say, to treat as MM) when FDG-PET/CT shows at least two hypermetabolic lesions and when the isFLC value is abnormal at diagnosis of SP, both predictors of early evolution to myeloma in our series. Surgery and/or radiotherapy would remain the appropriate therapeutic procedure for SP otherwise.

**Conclusion**

FDG-PET/CT and involved sFLC at diagnosis of SP are important predictors of the risk of progression to MM. Further studies are needed to confirm these factors, to consider developing a risk stratification model at diagnosis of SP, and then to determine whether a group of SP at high risk could benefit from an early systemic treatment rather than a local treatment, before transformation to MM.

**Disclosure of Potential Conflicts of Interest**

No potential conflicts of interest were disclosed.

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Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): G. Fouquet, S. Adib, T. Facon, D. Huglo, X. Leleu

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Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): C. Herbaux, S. Adib, O. Decaux, D. Huglo, X. Leleu

Study supervision: T. Facon, D. Huglo, X. Leleu

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Received October 28, 2013; revised March 18, 2014; accepted March 26, 2014; published OnlineFirst April 8, 2014.


Clinical Cancer Research

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Clin Cancer Res  Published OnlineFirst April 8, 2014.

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doi:10.1158/1078-0432.CCR-13-2910

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