Original Article

Long-lasting complete response to imatinib in a patient with systemic mastocytosis exhibiting wild type KIT

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Received August 18, 2014; Accepted October 10, 2014; Epub December 15, 2014; Published December 30, 2014

Abstract: Systemic mastocytosis (SM) is a hematopoietic disorder characterized by abnormal expansion of mast cells (MCs) in visceral organs. The skin is involved in most cases. In adult patients the transforming KIT mutation D816V is usually present and confers resistance against imatinib. Therefore, imatinib is not recommended for patients with KIT D816V+ SM. Nonetheless, imatinib may work in patients with SM lacking KIT D816V. However, little is known about long-term efficacy and safety of this drug in SM. We report on a 62-year-old female patient with indolent SM (ISM) who suffered from severe debilitating skin involvement despite therapy with anti-mediator-type drugs, psoralen and ultraviolet-A-radiation. Although multifocal MC infiltrates were detected in the bone marrow by immunohistochemistry, no KIT mutation was found by sequencing analysis. In 2003, treatment with imatinib (induction, 400 mg/day; maintenance, 200 mg/day) was initiated. During therapy, skin lesions and tryptase levels decreased. Treatment was well tolerated without any side effects. After 10 years, skin lesions have disappeared and the tryptase level is within normal range. This case-study confirms the long-term efficacy and safety of imatinib in patients with SM lacking activating KIT mutations. Imatinib should be considered in select cases of SM in whom MCs exhibit wild-type KIT.

Keywords: Mastocytosis, tryptase, KIT D816V, imatinib, long-term efficacy, drug safety

Introduction

Systemic mastocytosis (SM) is a heterogeneous group of hematopoietic disorders characterized by uncontrolled growth and expansion of neoplastic mast cells (MCs) in various organ systems, including the bone marrow (BM), skin, liver, spleen, and the gastrointestinal tract [1-4]. Based on the clinical course, organ involvement and signs of SM-related organ damage, indolent and advanced forms of the disease can be differentiated [1-4]. The consensus classification of the World Health Organization (WHO) discriminates between indolent SM (ISM), smouldering SM (SSM), aggressive SM (ASM), SM with an associated clonal hematologic non-MC-lineage disease (SM-AHNMD) and MC leukemia (MCL) [5-8]. In most adult patients with ISM, skin involvement is found and neoplastic cells display the transforming KIT mutation D816V [1-8]. Despite the presence of this oncogenic mutation, patients with ISM exhibit a normal or ‘near-normal’ life expectancy [9-11].

However, patients with ISM often suffer from severe mediator-related symptoms, a co-existing allergy or osteopathy [12-17]. In addition, patients with ISM experience cosmetic problems; and they may also suffer from the overwhelming skin involvement that may cause secondary problems such as local infections, blistering or even systemic adverse reactions [18-20]. In most patients, the trunk and the extremities are affected, whereas facial involvement is less frequently seen.

Treatment of ISM is usually based on ‘anti-mediator-type’ drugs and ‘MC-stabilizing’ agents [2-4, 12, 14, 19]. In patients with recurrent
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In the present study, we report on an ISM patient who suffered from severe treatment-resistant skin involvement, including debilitating facial lesions. In this unusual form of SM, no KIT mutation was found and the disease responded well to imatinib. After 10 years of treatment, the patient is free from any symptoms or side effects and exhibits a continuous complete regression of skin lesions and a normal tryptase level.

Case report and methods

Case report

A 62-year old female patient was referred in May 2003 because of mastocytosis with progressive skin lesions. She had been suffering from a generalized, maculopapular pigment-exanthema since 1980. Unlike in other patients with mastocytosis, the exanthema did not spare the facial skin. In 1991, a skin biopsy confirmed the diagnosis of mastocytosis (in the skin). In 1993, a BM examination was performed. However, no definitive signs of SM were detected and the final diagnosis of cutaneous mastocytosis, subtype urticaria pigmentosa (UP), was established. Because of skin symptoms (pruritus, erythema, edema) she was treated with psoralen and UVA radiation (PUVA) in 1986. PUVA therapy was repeated several times during the following years. In 1992 and 1993, she received interferon-alpha and glucocorticosteroids. In addition, she received anti-mediator-type drugs, including histamine receptor blockers. However, despite therapy, skin symptoms persisted and the skin lesions progressed in size and number. At admission in 2003, more than 80% of the total skin surface was affected, including not only the trunk, extremities and abdomen, but also the head and face (Figure 1). Unexpectedly, she did not suffer from systemic mediator-related symptoms. In addition, no lymphadenopathy or splenomegaly was found. Also, no allergy and no other relevant comorbidities were detected. In May 2003 BM examinations were repeated and revealed the diagnosis SM. The serum tryptase level amounted to 25.6 ng/ml. Blood counts and differential counts were normal. The sedimentation rate and the C reactive protein (CRP) were slightly elevated. All other laboratory parameters were normal. Based on physical examination, staging and laboratory parameters, the diagnosis ISM was established.

Figure 1. Immunohistochemical detection of neoplastic mast cells in the patient’s bone marrow (BM). BM sections were examined by indirect immunohistochemistry using an antibody against KIT (upper panel) and against tryptase (lower panel). Original magnification x 60. Note the presence of multifocal, perivascular accumulations of mast cells which is a pathognomonic feature and major criterion of systemic mastocytosis (SM).
Imatinib-induced remission in wt KIT SM

Treatment with imatinib and follow-up examinations

In November 2003, treatment with imatinib, 400 mg/day, was started. In April 2004, the dose of imatinib was reduced to 200 mg/day in order to minimize side effects and long-term risks. The patient was also treated with histamine receptor (HR) blockers, including the HR1 blocker desloratadine and the HR2 blocker ranitidine. Follow-up examinations included physical examination, a detailed inspection and photography of the skin, serum tryptase levels, complete blood counts and serum chemistry.

Immunohistochemistry

Immunohistochemistry was performed on paraffin-embedded and formalin-fixed BM sections obtained from the iliac crest in May 2003 following published protocols [31, 32]. Sections were stained with monoclonal antibodies (mAbs) directed against tryptase, chymase, KIT, CD25 and CD30 by indirect immunohistochemistry as reported [31, 32]. A specification of these mAbs is shown in Table 1.

Table 1. Specification of monoclonal antibodies (mAb) used for immunohistochemistry

<table>
<thead>
<tr>
<th>CD/Ag</th>
<th>Clone</th>
<th>Source</th>
<th>Isotype</th>
<th>mAb-Dilution</th>
<th>Retrieval</th>
<th>Provider</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD25/IL-2RA</td>
<td>IL-2R.1</td>
<td>mouse</td>
<td>IgG1</td>
<td>1:50</td>
<td>MW</td>
<td>Santa Cruz</td>
</tr>
<tr>
<td>CD30/Ki-1</td>
<td>Ber-H2</td>
<td>mouse</td>
<td>IgG1</td>
<td>1:20</td>
<td>MW</td>
<td>Dako</td>
</tr>
<tr>
<td>CD117/KIT</td>
<td>5F306</td>
<td>mouse</td>
<td>IgG1</td>
<td>1:100</td>
<td>MW</td>
<td>Dako</td>
</tr>
<tr>
<td>Tryptase</td>
<td>G3</td>
<td>mouse</td>
<td>IgG1</td>
<td>1:100</td>
<td>Proteinase</td>
<td>Cellmarque</td>
</tr>
<tr>
<td>Chymase</td>
<td>B7</td>
<td>mouse</td>
<td>IgG1</td>
<td>1:100</td>
<td></td>
<td>Millipore</td>
</tr>
</tbody>
</table>

Abbreviations: CD, cluster of differentiation; IL-2RA, interleukin-2-R-alpha; MW, microwave. Providers: Santa Cruz, Santa Cruz (CA, USA); Dako, Glostrup, Denmark; Cellmarque, Rocklin (CA, USA); Millipore, Temecula (CA, USA).

Molecular studies

BM and peripheral blood cells were examined for the presence of the KIT point mutation D816V by PCR analysis essentially as described [33-36]. In addition, the sequences of all exons of the KIT gene were analysed in BM-derived DNA by Sanger sequencing.

Results

Morphologic and histologic findings

The BM smear showed a normocellular marrow with regular distribution of white blood cells and precursor cells, no increase in blast cells, no signs of dysplasia and a MC count of 2%. These MCs exhibited an atypical, spindle-shaped, morphology with oval nuclei and a hypogranulated cytoplasm. The BM histology confirmed the presence of atypical MCs. These MCs were found to form small clusters and aggregates in tryptase-stained BM sections, fulfilling the major diagnostic criterion of SM (Figure 2). MCs stained positive for tryptase, KIT and CD25 but did not react with an antibody against CD30 (Table 2). The infiltration grade with neoplastic MCs was 5%. No signs of an additional myeloproliferative or myelodysplastic BM disorder were found. The serum tryptase in May 2003 was elevated (25.6 ng/ml), confirming the presence of SM. No signs of organomegaly or organ damage caused by the MC infiltrates were found. Based on these findings, the final diagnosis ISM was established.

Molecular findings and sequencing results

As assessed by mutation-specific clamping PCR, BM cells did not express KIT mutations in codon 816. We therefore extended our investigations to Sanger sequencing of all KIT exons. However, again, no KIT mutation was found. We were also unable to detect any other molecular lesions by PCR, including JAK2 V617F.

Clinical and hematologic response to imatinib

The patient responded well to imatinib. Within the first 6 months, skin lesions decreased in size, and the symptoms (itching, flushing) also improved substantially. In May 2003 the dose of imatinib was reduced to 200 mg/day. After one year, the response was classified as good partial response. At that time, a partial regression of skin lesions was seen (Figure 1). Over the next few years, the patient’s condition further improved, and the number of skin lesions further decreased. In addition, the serum tryptase level decreased to normal range (< 15 ng/ml). The patient did not suffer from any side effects. After 10 years of observation, skin lesions have disappeared and the response was classified as major response (MR) with complete regression of skin lesions. Unfor-
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![Figure 2. Facial skin lesions in patient with mastocytosis. Facial skin was examined and photographed before treatment with imatinib (left panel) and one year after therapy with imatinib (right panel). The loading dose of imatinib (5 months) was 400 mg/day, and maintenance dose 200 mg/day.](image)

**Table 2.** Immunophenotype of neoplastic mast cells in the patient’s bone marrow sections

<table>
<thead>
<tr>
<th>Antigen</th>
<th>CD</th>
<th>The patient’s BM MCs</th>
<th>MCs in patients with ISM</th>
<th>MCs in patients with ASM *</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-2RA</td>
<td>CD25</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Ki-1</td>
<td>CD30</td>
<td>-</td>
<td>+/-</td>
<td>+</td>
</tr>
<tr>
<td>KIT</td>
<td>CD117</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Tryptase</td>
<td>n.c.</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Chymase</td>
<td>n.c.</td>
<td>+/-</td>
<td>+/-</td>
<td>-</td>
</tr>
</tbody>
</table>

Data were obtained by indirect immunohistochemistry using antibodies directed against various leukocyte (differentiation) antigens. BM, bone marrow; MCs, mast cells; ISM, indolent SM; ASM, aggressive SM; IL-2RA, interleukin-2 receptor alpha chain; n.c., not yet clustered. *Data refer to the published literature.

Unfortunately, however, we were unable to re-examine the BM to confirm a complete hematologic remission (CR).

**Discussion**

Treatment of mastocytosis usually has to be adjusted to a number of disease-specific and patient-related variables, including the KIT mutation status, presence of signs and symptoms of organ damage, and comorbidities [1-4, 7, 12]. In many cases, prophylactic and symptomatic treatment with anti-mediator-type drugs are sufficient to keep SM-related symptoms under control [3, 12, 19]. In other patients, additional therapy may be required. In those with advanced SM, cytoreductive therapy is often recommended [1-4, 37]. More recently, treatment with KIT-targeting TKI has been proposed [28-30]. However, the KIT mutation D816V confers resistance against imatinib [25, 26]. Thus, imatinib cannot be recommended for most patients with SM as these patients usually exhibit KIT D816V. In this study, we present a case of ISM in whom treatment with imatinib induced a complete disappearance of skin lesions, a complete resolution of all symptoms as well as a decrease in serum tryptase levels to normal range. Sequencing of KIT confirmed that in this patient, neoplastic MCs did not exhibit KIT D816V. After 10 years of observation, the patient still has a major response without any drug-related side effects. This case confirms the remarkable efficacy and long-term safety of imatinib in such patients.

The diagnosis of SM is based on major and minor SM criteria. The major criterion relates to the multifocal cluster-formation of MCs in BM sections [5-8, 38]. Minor SM criteria include morphologic atypias of MCs, expression of CD2 and CD25, and expression of an activating KIT mutation in codon 816 [5-9]. In our patient, the major SM criterion as well as all minor SM criteria were met, and no signs of advanced SM were found, so that the final diagnosis of ISM was established. In this regard it is noteworthy that the massive local infiltration of the skin by atypical MCs does not qualify as criterion of advanced SM. Rather the skin lesions are more frequently detectable in ISM whereas in patients with advanced SM, such as ASM or MCL, skin lesions are often absent [5-8].

Skin involvement in SM can manifest in various clinical and morphologic patterns, ranging from small-sized flat lesions without any symptoms to nodular or plaque forms, accompanied by massive clinical symptoms, such as flushing, itching or blistering [18-20, 38, 39]. In most SM patients, the exanthema spreads over the trunk...
and extremities, but (typically) spares the face. In our patient, massive skin involvement with accompanying clinical symptoms was recorded. Despite therapy with anti-mediator-type drugs and interferon-alpha, skin lesions not only persisted but increased in number and size over time and caused progressive symptoms. A remarkable aspect was that the mastocytosis lesions were even detectable and prominent in the facial skin. Whether this unusual distribution is related to a certain molecular pattern or mutation in critical target genes remains unknown.

In most patients with SM, the activating KIT mutation D816V is detected in neoplastic cells [4-6, 33-36, 40]. Even in patients with a low burden of MCs, these cells usually display KIT D816V. In our patient, we were not able to detect a KIT mutation at codon 816 by using a highly sensitive PCR (detection level: 1 mutated cell out of 1,000 normal cells) [36]. Therefore, sequencing of the entire exon-sequence of KIT was performed using cells derived from BM sections. However, again, no activating mutation in KIT was detected which fits well with the very good response to imatinib seen in this patient. In fact, it has been described that wild type KIT and a few known KIT mutant-forms are sensitive to imatinib [4, 25, 27]. An alternative explanation for the good response would be that neoplastic cells exhibited an imatinib-responsive KIT mutant that was not detected in the BM samples because of the small size of the clone and the relatively low sensitivity of the Sanger sequencing method.

Besides imatinib, a number of different KIT inhibitors have been developed, including dasatinib and midostaurin (PKC412). The disadvantage of imatinib is that the recurrent KIT mutation D816V confers resistance [25, 26]. The advantage of imatinib is its well-documented long-term safety recorded in patients with chronic myeloid leukemia (CML). The advantage of midostaurin and dasatinib is that the D816V-mutated form of KIT is sensitive against both drugs [26, 41, 42]. However, both drugs have side effects, and only limited data concerning the long-term safety of these agents are available. Especially dasatinib may cause problems, such as recurrent pleural effusion. Therefore, it seems clear that for patients in whom the disease is aggressive and no mutation in codon 816 of KIT is found, imatinib is the preferred kinase blocker. By contrast, in patients with advanced SM exhibiting KIT D816V, midostaurin is a preferred agent as cells are resistant against imatinib.

So far, only a very few reports on SM patients treated with imatinib have been presented [28-30]. In most of these cases, no long-term observational data were reported. Therefore, it remains unknown whether imatinib can be regarded as an effective and safe drug in all patients with SM, especially when administered on a life-long basis. The long-term efficacy of imatinib was nicely demonstrated in our patient with ISM which can be explained by the absence of resistance-mediating KIT mutations. However, it was also very important to learn that imatinib did not produce any clinically relevant side effects after an observation period of 10 years. These observations support the use of imatinib in these patients.

As mentioned above imatinib was found to exert major clinical effects in our patient with SM. Based on established response-criteria [42] the response in our patient was classified as a major clinical response with complete regression of all SM-related findings and symptoms. In addition, we found that the serum tryptase level returned to normal range and the skin lesions regressed. Therefore, it seems likely that the drug also produced a complete hematologic remission (CR) in our patient. However, unfortunately, we were unable to proof a CR because we were unable to take a second BM biopsy. From serum tryptase levels it seems even likely that most neoplastic and also many normal MCs were depleted by the long-term treatment with imatinib.

In summary, we show that long-term treatment with imatinib in SM patients with wild type KIT is an effective and probably safe approach that can be recommended for certain cases with otherwise resistant disease requiring anti-SM therapy.

Acknowledgements

This study was supported by the Austrian National Science Fund (FWF), grant #SFB-F4704-B20.

Disclosure of conflict of interest

PV. is a consultant in a global Novartis trial examining the effects of PKC412 (midostaurin) in advanced mastocytosis. PV. received a...
research grant from Novartis and a research grant from The Mastocytosis Society.

Abbreviations

AHNMD, associated hematologic non-mast cell lineage disease; ASM, aggressive systemic mastocytosis; CM, cutaneous mastocytosis; ISM, indolent systemic mastocytosis; MC, mast cell; SM, systemic mastocytosis; SSM, smoldering systemic mastocytosis; TKI, tyrosine kinase inhibitor; WHO, World Health Organization.

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