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Response of patients with indolent systemic mastocytosis to tamoxifen citrate

Joseph H. Butterfield (MD)[a,c,*], Dong Chen (PhD)[b,c]

[a] Division of Allergic Diseases, Mayo Clinic, Rochester, MN, United States
[b] Division of Hematopathology, Mayo Clinic, Rochester, MN, United States
[c] The Mayo Clinic Program for Mast Cell and Eosinophil Disorders, United States

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ABSTRACT

We examined whether tamoxifen citrate at 20 mg/day for 1 year had a beneficial effect on laboratory findings, bone marrow mastocytosis, common clinical symptoms, or quality-of-life assessment for 5 women and 2 men with indolent systemic mastocytosis. Tamoxifen was well tolerated. We found significant reductions in the platelet count, serum alkaline phosphatase, and 24-h urinary excretion of *N*-methylhistamine and significant increases in serum lactate dehydrogenase and (excluding 2 patients taking aspirin) in 24-h urinary excretion of 11β-prostaglandin $F_{2\alpha}$. Overall, no change occurred in percent involvement of bone marrow by mastocytosis. Symptom scores were mild and did not change during the treatment. The 36-Item Short Form Health Survey scores for quality of life physical and mental components showed no marked changes. Tamoxifen, an older, nonhematotoxic medication, has limited activity in systemic mastocytosis at the dosage used in this study.

1. Introduction

Systemic mastocytosis (SM) is a clonal mast cell (MC) proliferative disorder with extracutaneous involvement and MC mediator-related symptoms. Current treatment recommendations for control of mediator-related symptoms entail use of $histamine_1$ and $histamine_2$ receptor antagonists, oral sodium cromolyn, proton pump inhibitors, anticholinergic agents, aspirin, bisphosphonates (for bone pain and osteoporosis), and glucocorticoids alone and in combination, depending on the patient's particular symptom complex [1–6]. However, none of these agents reduces the proliferating MCs in the involved organs. Currently, no guidelines provide the "best" time to initiate SM treatment with agents to reduce the disease burden of clonal cells.

Patients with aggressive SM, with SM associated with clonal, hematologic non-MC disease, or with MC leukemia generally are considered candidates for cytotoxic agents because of associated findings indicating impaired organ function. These "C findings" include cytopenias, hepatomegaly with ascites and impaired liver function, splenomegaly with associated hypersplenism, malabsorption, skeletal lesions (e.g., osteolyses, pathologic fractures) due to severe osteoporosis, and life-threatening organopathy elsewhere [7]. SM patients also can be considered for cytoreductive treatment when mediator-related symptoms no longer can be controlled with tolerated doses of such medications as those mentioned.

Available cytoreductive medications for treating SM include interferon α-2b [8], 2-chlorodeoxyadenosine [9], and imatinib mesylate (for SM without the *KIT* Asp816Val mutation) [10]. Besides midostaurin, [11] which has proven effectiveness in advanced SM, many agents active in vitro have yielded only limited [12] or no benefit clinically [13–15]. Use of these agents has been restricted by such adverse effects as cytopenias or by clinical intolerance. In advanced SM, the associated cytopenias can limit the medication dose and thus can reduce the chance of successful treatment. Therefore, the availability of an agent that can decrease MC disease burden but is largely free of clinical or bone marrow adverse effects could advance treatment of this disorder. Moreover, treatment of SM in its early stages – when the MC burden is less – may have a better chance for a durable response than late-stage treatment.

In vitro studies of the HMC-1 human MC leukemia cell line have showed that tamoxifen (concentration, 30 mmol/L) produces a mean (SD) dose-dependent inhibition of proliferation of 90.3%

Abbreviations: 11β-$PGF_{2\alpha}$, 11β-prostaglandin $F_{2\alpha}$; MC, mast cell; MCS, mental component score; MPCM, maculopapular cutaneous mastocytosis; *N*-MH, *N*-methylhistamine; PCS, physical component score; QOL, quality of life; SF-36, 36-Item Short Form Health Survey; SM, systemic mastocytosis.

* Corresponding author at: Division of Allergic Diseases, Mayo Clinic, 200 First St SW, Rochester, MN 55905, United States. Fax: +1 507 284 0902.
E-mail address: butterfield.joseph@mayo.edu (J.H. Butterfield).

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(4.0%) without altering cell viability. This effect was associated with a reduction of the outward chloride ion current and a simultaneous opening of a novel, inwardly rectifying, nonselective cation current [16]. In the present study, we examined the effect of a 1-year course of tamoxifen on the levels of MC mediators, degree of bone marrow involvement and symptoms, and quality-of-life (QOL) scores in SM.

2. Methods

2.1. Patient selection

Patients meeting the 2001 World Health Organization criteria for SM [17] were invited to participate in the study. No subtype of SM was excluded from potential enrollment. Each patient completed the patient consent form before enrollment. The Mayo Clinic Institutional Review Board approved the study.

2.2. Clinical and laboratory evaluation

A complete physical examination was performed before and after 6 and 12 months of tamoxifen 20 mg orally per day. Papanicolaou smears and pelvic examinations were performed on female participants before and after 12 months' treatment. Bone marrow aspiration and biopsy and computed tomography of the abdomen and pelvis were obtained on all participants before and after 12 months' treatment. Bone marrow biopsy specimens were stained for MC infiltrates with tryptase immunostaining. Presence of the *KIT* Asp816Val mutation was tested with qualitative, allele-specific polymerase chain reaction as previously described [18].

Complete blood cell count with leukocyte differential and platelet count and testing for alkaline phosphatase, hemoglobin, lactic dehydrogenase, serum tryptase, and 24-h urinary excretion of *N*-methylhistamine (*N*-MH) and 11β-prostaglandin $F_{2\alpha}$ (11β-$PGF_{2\alpha}$) were monitored before the study and after 6 and 12 months of tamoxifen therapy. Urinary 11β-$PGF_{2\alpha}$ was measured by direct immunoassay (11β-$PGF_{2\alpha}$ EIA *KIT*; Cayman Chemical) and urinary *N*-MH by liquid chromatography–tandem mass spectrometry on 24-h urine collections [19]. Women of child-bearing potential had pregnancy testing before enrollment.

We constructed a symptom questionnaire containing 27 symptoms commonly experienced by SM patients (including an open category for "other" symptoms). Severity of each symptom was rated from 0 to 10 (0, absence of symptom; 1–4, mild symptoms; 5–7, moderate symptoms; 8–10, severe or intolerable symptoms). Individual symptoms were categorized into 6 domains, within which an overall mean score was calculated for each patient. The domains were as follows:

- Cardiovascular (loss of consciousness or fainting, rapid heartbeat).
- Skin (flushing or hives, generalized or localized swelling, bruising).
- Neurologic (headaches, forgetfulness, depression, dizziness).
- Gastrointestinal (weight loss, abdominal pain or bloating, indigestion, constipation, diarrhea, rectal bleeding, stomach ulcer, nausea, vomiting).
- Musculoskeletal (spinal, rib, hip, or muscle pain; bone fracture).
- Upper airway (throat tightness).

The mean score for each symptom domain was calculated monthly and end-of-study average score was compared with start-of-study average score for the group as a whole.

In addition, the 36-Item Short Form Health Survey (SF-36) [20] was completed before the start of tamoxifen treatment and at every month during the study. The individual SF-36 subscales have a possible range from 0 to 100 (pain index, general health perceptions, mental health index, physical functioning, role-emotional, role-physical, social functioning, and vitality). We calculated subscales, average mental component score (MCS), and physical component score (PCS). These scores are standardized to a population mean (SD) score of 50 (10). Scores less than 50 indicate lower QOL than the population on average. Medication use of each patient was also recorded.

2.3. Statistical analysis

The percentage change from baseline to follow-up in laboratory measures was assessed with paired *t* tests. *P* values <.05 were considered statistically significant.

3. Results

Seven patients enrolled in the study. Although patients with any of the subtypes of SM were eligible, all patients who eventually enrolled in this study were classified as having indolent SM. All completed 12 months of treatment without untoward effects. A summary of patient demographic characteristics appears in Table 1.

3.1. Patient histories

Patient 1 was a 48-year-old woman with both a 4-year history of skin pruritus, flushing, and hives with maculopapular cutaneous mastocytosis (MPCM) confirmed through skin biopsy and a 2-year history of diarrhea and anemia (from menorrhagia). Bone marrow biopsy obtained several years previously showed involvement of mastocytosis; a serum tryptase level was more than 4 times the upper limit of normal, and testing for random urinary histamine and 24-h urine *N*-MH showed increased values. While taking tamoxifen, the patient had decreased frequency of diarrhea

Table 1
Patient demographic characteristics.

Patient no.	Age, y/sex	Presence of MPCM, duration	Symptoms	Prior chemotherapy	Mastocytosis medications	Smoker	Atopic disorders
1	48/female	Yes, 4 y	P, F, D, FAT	None	CH	No	None
2	49/female	Yes, 18 mo	None	None	L, A (during study)	No	None
3	39/male	Yes, 12 y	F, D, T	None	CH, A, M, UVA	Yes, 1 ppd	Allergic rhinitis
4	55/female	None	ANA, S, P, FAT	None	FEX	No	Asthma, allergic rhinitis, cold urticaria
5	36/male	Yes, 12 y	P, PS, D, C, V, BF	None	CH, R, DX, A	No	None
6	42/female	Yes, 31 y	P, S, D, B	IFN	DX, FEX, A, L	No	None
7	53/female	Yes, 20 y	FI, P, F, SW, D, V, H/A, BL, T	None	A, DX, CH	Yes, 1–2 ppd	None

Abbreviations: A, aspirin; ANA, anaphylaxis; B, bursitis; BF, brain fog/memory; BL, bloating; C, constipation; CH, cetirizine hydrochloride; D, diarrhea; DX, doxepin; F, flushing; FAT, fatigue; FEX, fexofenadine; FI, flying insect reaction; H/A, headache; IFN, interferon α-2b; L, loratadine; M, metoprolol; MPCM, maculopapular cutaneous mastocytosis; P, pruritus; ppd, pack per day; PS, presyncope; R, ranitidine; S, swelling; SW, sweats; T, tachycardia; UVA, UVA-1 phototherapy; V, vertigo.