

Response of patients with indolent systemic mastocytosis to tamoxifen citrate



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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 11 β -prostaglandin F_{2 α} . 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.

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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 histamine₁ and histamine₂ 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: 11 β -PGF_{2 α} , 11 β -prostaglandin F_{2 α} ; 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.

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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 11 β -prostaglandin $F_{2\alpha}$ (11 β -PGF $_{2\alpha}$) were monitored before the study and after 6 and 12 months of tamoxifen therapy. Urinary 11 β -PGF $_{2\alpha}$ was measured by direct immunoassay (11 β -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 heart-beat).

- 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, buritis; 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.

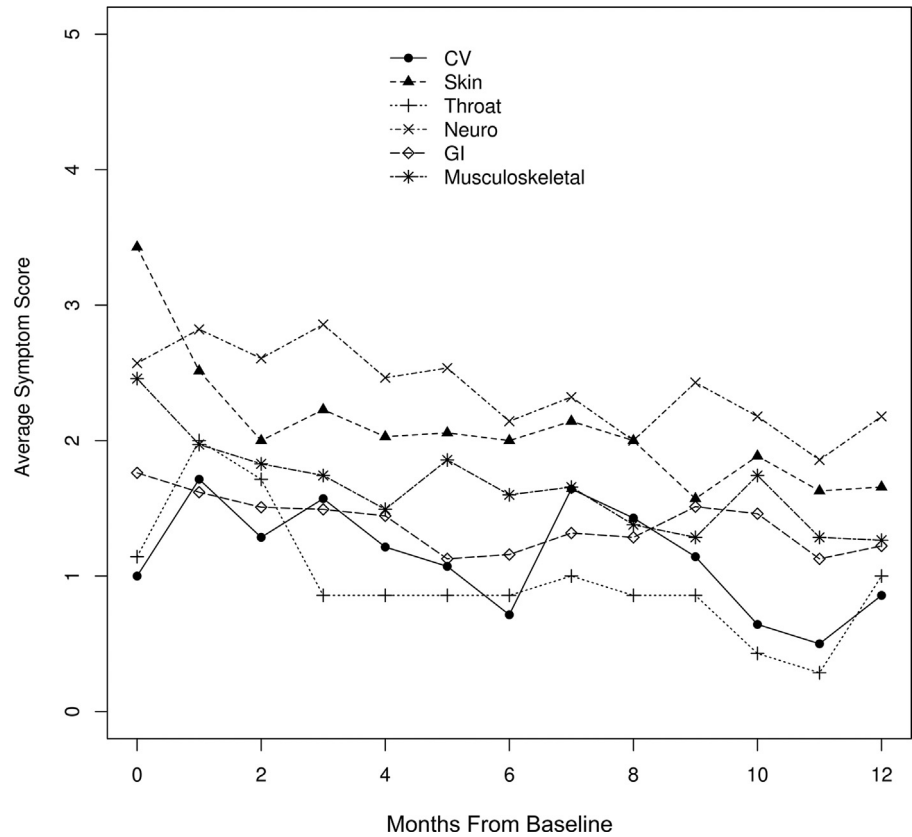


Fig. 1. Average symptom scores by time of study ($N=7$). Possible symptom score is from 1 to 10. CV indicates cardiovascular; GI: gastrointestinal; neuro: neurologic.

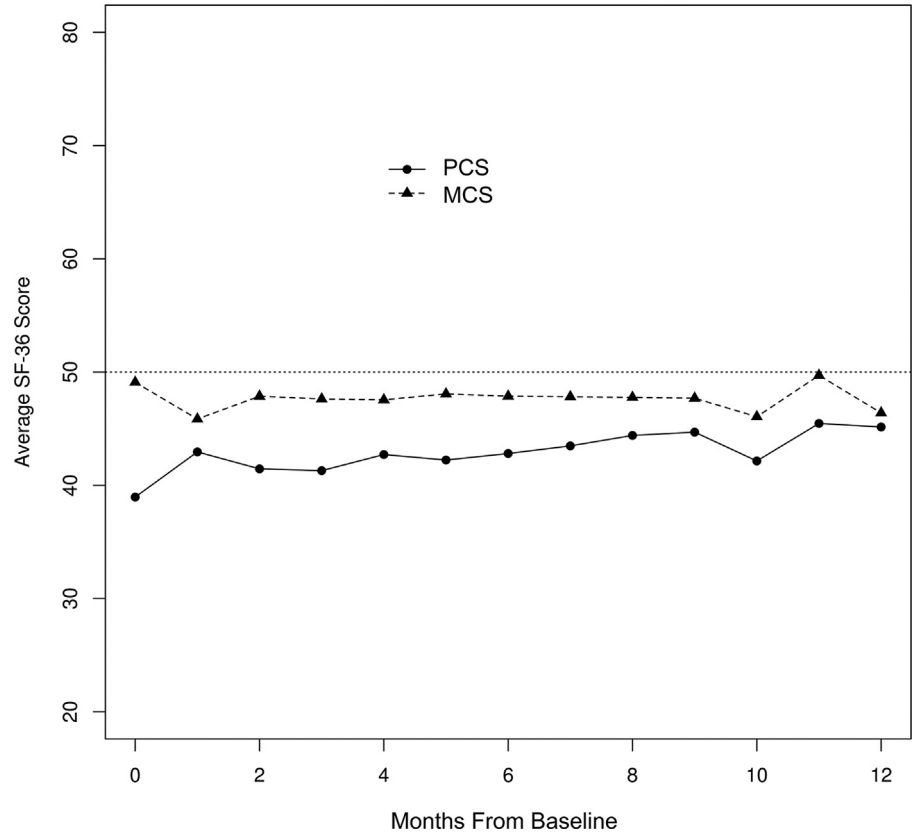


Fig. 2. Average SF-36 Score by time of study for PCS and MCS Parameters for Quality of Life ($N=7$). Population average score is 50. MCS indicates mental component score; PCS: physical component score; SF-36: 36-Item Short Form Health Survey.

Table 2
Laboratory results of the 7 patients in the study.

Test (reference range)	Patient 1			Patient 2			Patient 3			Patient 4			Patient 5			Patient 6			Patient 7		
	Start	6 mo	End	Start	6 mo	End	Start	6 mo	End	Start	6 mo	End	Start	6 mo	End	Start	6 mo	End	Start	6 mo	End
CBC																					
Hemoglobin (120–155 g/L for women; 135–175 g/L for men)	11.3	11	10.1	14.9	13.7	13.8	13.6	14.6	14.9	14.1	13.6	13.9	15.4	16.3	16.2	13.2	13	12.6	15.3	14.9	14.2
Leukocytes ($3.5\text{--}10.5 \times 10^9/\text{L}$)	9.9	6.5	8.1	7.1	8.2	8	7.8	8.1	6	7	6.7	4.8	6.6	7.6	12.7	6	5.7	4.7	10.6	9.8	8.6
Platelet count ($150\text{--}450 \times 10^9/\text{L}$)	467	412	397	341	299	282	300	282	286	233	224	233	176	176	182	217	195	183	257	242	243
Chemistry values																					
Alkaline phosphatase ($0.5\text{--}2.0 \mu\text{kat/L}$)	1.49	1.1	0.95	1.42	1.17	0.65	1.17	0.99	1.35	1.28	.952	.799	.782	.816	.799	1.39	1.11	1.0	1.65	1.29	1.34
Lactate dehydrogenase ($122\text{--}222 \text{ U/L}$)	84	105	115	167	176	176	127	170	169	78	105	99	118	131	141	95	100	98	195	177	176
Tryptase ($<11.5 \text{ ng/mL}$)	69.4	69.1	61.9	27.2	25	28.4	118	117	100	81.3	78.5	68.3	88.5	76.3	87	27.1	31.7	31.6	69.1	56.8	68.7
N-MH (30–200 mcg/g creatinine)	1410	1035	1,056	345	319	288	913	567	860	268	236	208	1565	1583	1333	331	311	364	960	896	765
11 β -PGF _{2α} ($<1000 \text{ ng/24 h}$)	3479	4135	5268	2747	377	278	1663	<140	165	368	268	208	3310	8738	4914	305	167	459	673	551	603
Bone marrow mast cell involvement (%)	5–10	NA	5–10	10	NA	5–10	30	NA	20–30	<5	NA	<5	20–30	NA	20	5	NA	5	15	NA	5–10
CT of abdomen and pelvis	Neg	NA	Neg ^a	Neg	NA	Neg ^b	Neg	NA	Neg	Neg	NA	Neg	Neg	NA	Neg	Neg	NA	Neg	Neg	NA	Neg

Abbreviations: CBC, complete blood cell count; CT, computed tomography; 11 β -PGF_{2 α} , 11 β -prostaglandin F_{2 α} ; N-MH, N-methylhistamine; NA, not available; Neg, negative.

^a Accessory spleen.

^b Bilateral adnexal cyst.

but had no change in the extent of her cutaneous mastocytosis. Her serum tryptase level decreased by 11% during the year of treatment.

Patient 2 was a 49-year-old woman who was seen 18 months after skin lesions developed on both thighs, the biopsy of which showed cutaneous mastocytosis. SM was confirmed with bone marrow biopsy, which showed 10% involvement by mastocytosis. She had no symptoms of MC activation. She was treated with loratadine (10 mg/day) and was instructed in the use of a self-administered epinephrine injector. The patient's physical examination at our clinic showed lesions of MPCM on the anterior and inner thighs and anterior abdominal wall. Urinary excretion levels of *N*-MH and 11β -PGF $_{2\alpha}$ were elevated, as was the serum tryptase level. She began taking aspirin (325 mg/day) and, subsequently, tamoxifen (20 mg/day). The appearance of her cutaneous mastocytosis lesions did not change. Her serum tryptase value was increased modestly (by 4.4%) at study completion, but the excretion of *N*-MH decreased by 16.5%. During the years following the study, the patient's serum tryptase value subsequently decreased by 37% and *N*-MH excretion decreased by an additional 18% compared with end-of-study values.

Patient 3 was a 39-year-old man with a 12-year history of generalized cutaneous mastocytosis. He had flushing for most of his life, aggravated by alcohol ingestion. He reported occasional episodes of diarrhea but no cramps or weight loss. Routine medications included cetirizine hydrochloride (10 mg/day) for nasal allergy and aspirin (81 mg/day) for cardiovascular prophylaxis. Physical examination showed diffuse lesions of cutaneous mastocytosis on the trunk and extremities. He had no organomegaly or bone pain. While taking tamoxifen, he believed that his episodes of diarrhea lessened and gastroesophageal reflux symptoms improved. We were able to monitor this patient's mediator levels for several years following completion of the study and found that after 5.5 years, the serum tryptase decreased by an additional 34% and *N*-MH excretion decreased by an additional 24%.

Patient 4 was a 55-year-old woman with symptoms of swelling and anaphylaxis for 10–11 months following a hysterectomy. She had a long history of cold urticaria controlled with fexofenadine. She denied flushing, swelling, or loss of consciousness. Osteopenia was treated with alendronate sodium, calcium, and vitamin D. During the study, she continued to use an estradiol patch. She had 5–10% involvement of her bone marrow by mastocytosis and had positivity for the *KIT* Asp816Val mutation. While taking tamoxifen, she had less fatigue, bruising, erythema, and pruritus. Although both tryptase and *N*-MH values decreased during tamoxifen administration, poststudy follow-up showed further decreases of 17% and 15%, respectively.

Patient 5 was a 36-year-old man with a 12- to 13-year history of MPCM and an initial bone marrow biopsy positive for 15–20% involvement by mastocytosis. He reported intense pruritus aggravated by heat, severe arthralgias of the feet, vertigo and presyncope, and intermittent constipation with diarrhea. Trials of quercetin and rhodiola flavonoids, ketotifen, and oral cromolyn sodium were not beneficial to his symptoms. Tamoxifen was continued for 1 year without adverse effects, and at the conclusion of this study, he noted resolution of vertigo and less arthritic pains. Memory problems did not improve; however, he felt overall improved.

Patient 6 was a 42-year-old woman with a history of MPCM since age 9 years. Over that time, the lesions had become extensive and confluent over large areas of her body. Initial bone marrow biopsies performed in 1991 and 1998 failed to detect lesions of SM; however, subsequent biopsies did show characteristic lesions involving 5% of the bone marrow. Past cytoreductive treatment of SM included high-dose interferon α -2b (5 million units, and then 10 million units, 3 times per week) taken for 18 months. Ongoing symptoms at the time of study enrollment included pruritus, swelling of hands and feet, bilateral trochanteric bursitis, and 5 or

6 episodes of diarrhea per day. She completed 1 year of the tamoxifen treatment without adverse effects. While taking tamoxifen, she noted markedly less diarrhea but increased hip pain, flushing, and itching.

Patient 7 was a 53-year-old woman with a history of MPCM for more than 20 years. She had a systemic reaction to a flying insect sting about 10 years previously and had undergone a cardiac ablation procedure for recurrent episodes of paroxysmal atrial tachycardia 5 years previously. Her ongoing symptoms included itching, flushing, sweating, diarrhea, vomiting, gastroesophageal reflux disease, postprandial bloating, headaches, fatigue, dizziness, osteopenia, and episodic tachycardia. She was a smoker of 1–2 packs of mentholated cigarettes per day since age 14 years. During her 1-year tamoxifen course, she was treated in an emergency department setting for a sensation of throat swelling after taking guaifenesin and had a tibial fracture following a high-impact injury. Symptomatically, she felt little different at the end of the 1 year; however, she had modest reductions in her excretion of *N*-MH and 11β -PGF $_{2\alpha}$.

3.2. Symptom scores

Overall, the average symptom scores across the 7 patients were within the mild range (i.e., scores of 1–4) across all domains and time points. The symptom domains that scored most highly at baseline were skin (mean, 3.4), neurologic (mean, 2.6), and musculoskeletal (mean, 2.5). The other domains had lower reported symptoms at baseline: gastrointestinal (mean, 1.8), upper airway (mean, 1.1), and cardiovascular (mean, 1.0). In general, the average score within most domains decreased over time, with average scores of 2.2 (neurologic symptoms) or lower (all remaining <2) at the last follow-up (Fig. 1).

Considering the symptoms individually, most symptoms were rated at or below mild (score, 1–4) on average across all time points with a few exceptions: flushing (mean score, 5 at baseline), hives (mean score, 6 at baseline), constipation (mean score, 4–5 at first follow-up), and muscle pain (mean score, 4–5 at baseline).

3.3. Quality of life

The SF-36 is a questionnaire designed to assess overall QOL, including physical and emotional health [20]. Data are divided among 8 scales. A 0.5-SD difference in QOL outcomes has been shown to be clinically significant [21]. With SF-36 PCS and MCS, this SD level corresponds to a 5-point change in outcome (population mean [SD], 50 [10]). In addition, for each scale of the SF-36, higher scores correspond to better health. During the 12 months of tamoxifen treatment, although the PCS and MCS were lower than the population average in general, the average PCS did increase by 6 points (from 39.0 to 45.1), indicating improvement in physical QOL. The MCS decreased by a small amount (from 49.1 to 46.4) but remained relatively flat during the majority of follow-up months (Fig. 2). When considering the more specific QOL subdomains, 4 patients reported a decrease of at least 5 points in the bodily pain scale (range, –9 to –16 points), indicating that pain actually increased over time (Fig. 2).

Two patients had improvement in pain: Patient 6 improved by 30 points (from 22 to 52) and patient 7 by 10 points (from 41 to 51). Large differences were observed for 2 patients with respect to improved general health perception: Patient 1 improved by 30 points (from 42 to 72) and patient 5 by 20 points (from 32 to 52).

3.4. Laboratory results

Table 2 summarizes the pretreatment, 6-month, and end-of-study (1-year) results for hematology, chemistry, and urine

mediator levels of the 7 patients. From pretreatment to the end of study, no significant changes occurred in hemoglobin levels, total leukocyte counts, or serum tryptase levels. Significant changes were found in the values of platelet counts (-7.8% , $P=.01$), serum alkaline phosphatase (-15.6% , $P=.04$), serum lactate dehydrogenase ($+16.5\%$, $P=.01$), 24-h urinary excretion of *N*-MH (-13.6% , $P=.003$), and 24-h urinary excretion of 11β -PGF $_{2\alpha}$ ($+32.3\%$, $P=.007$). Tryptase-stained bone marrow biopsy results obtained before and after tamoxifen therapy are also shown. Overall, no substantial change was seen in the percentage of bone marrow involvement by mastocytosis.

4. Discussion

Tamoxifen was well tolerated, simple to administer, and inexpensive to use. Patient compliance was excellent. With the exception of midostaurin (PKC412), therapeutic trials in SM have yielded disappointing clinical results [10,11,22–25]. Alternative treatment approaches to control MC proliferation that do not target the *KIT* mutation are warranted. Tamoxifen, currently used primarily for breast cancer chemoprevention, is an older medication with known safety and adverse effect profiles. An advantage to tamoxifen use is that the occurrence of hematologic adverse effects, such as thrombocytopenia or leukopenia, is rare compared with chemotherapeutic agents [26].

MCs are long-lived cells [27,28]. Studies of other agents used in treatment of SM have shown that prolonged high-dose treatment may be necessary to effect a substantial change in mediator levels and bone marrow involvement [29–31]. Serum tamoxifen levels of women given this medication at the dose used in this study (20 mg/day) have been reported elsewhere (mean [range], 83.6 [8.7–134.4] ng/mL) [32]. These reported serum values, on a molar basis, are 0.075–12% of the tamoxifen concentrations previously used in an in vitro study that showed the growth inhibitory effect on HMC-1 cells [16]. Despite these reported low serum levels of tamoxifen, human and rat studies involving malignant and non-malignant tissues showed levels of tamoxifen and its metabolites between 10 and 60 times those of serum levels [33]. This reported presence of high concentrations of tamoxifen in tissue such as liver [33] could be advantageous when treating tissue-infiltrating MCs. Nevertheless, it is uncertain whether tamoxifen is enriched in SM tissues such as skin and bone marrow. If tamoxifen has low local tissue distribution in skin or bone marrow, high-dosing strategy can be used, as in treating other malignancies, including hormone refractory prostate cancer. At that dose (160 mg/m²/day), micromolar serum concentrations of tamoxifen and a 23% response rate were achieved [34].

The present study showed that tamoxifen administered at 20 mg/day was well tolerated but did not significantly improve tryptase levels or bone marrow involvement by SM after 1 year. There are 2 possibilities for this result: (1) inadequate local tissue tamoxifen concentration that is sufficient to cause MC cytorreduction, and (2) the previous in vitro study of tamoxifen [16] used immature MCs from an MC leukemia line having 2 *KIT* mutations, Asp816Val and Val560Gly. None of the patients in the present study had MC leukemia, and only the Asp816Val mutation was examined.

Tamoxifen at 20 mg/day appears to have an inhibitory effect on MC mediator secretion. Laboratory studies obtained for 3 patients following conclusion of the formal study showed continued decrease in tryptase and *N*-MH levels. This MC secretion inhibition effect was noted in a previous report in an animal study [35]. The prolonged effect, even after the termination of the study, is possibly caused by continued release of tamoxifen from tissue such as liver.

Symptoms reported by the enrolled patients were generally mild and rarely moderate in severity. All of our patients were classified as having indolent SM. Symptom scores were improved in many patients. The QOL assessment showed a modest improvement in PCS after 1 year of tamoxifen treatment, and the MCS decreased slightly. These improvements could be related to MC mediator secretion inhibition. An alternative explanation is that tamoxifen has antagonistic activity to histamine [36].

In summary, this study failed to demonstrate effective cytorreduction activity of tamoxifen at a dose of 20 mg/day. However, it does show possible MC secretion or mediator antagonizing effects. Further studies, including nonindolent forms of SM, are needed to confirm these findings and to optimize tamoxifen dosing to achieve possible cytorreduction effect in both indolent and other variants of SM.

Conflicts of interest

None.

Funding source

None.

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