



REVIEW ARTICLE

Cladribine in the Treatment of Systemic Mastocytosis, a Review of the Literature

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Abstract

Mastocytosis is a rare disease for which treatment with cladribine (2-chlorodeoxyadenosine) was first reported in 2001. Cladribine has meanwhile been administered in over hundred reported cases and is available for intravenous and subcutaneous administration. Cladribine has mainly been used in systemic mastocytosis and in larger series responses were obtained in over 50% of cases in which treatment with H1/H2 blockers, interferon or tyrosine kinase inhibitors did not induce a response. Literature describing the use of cladribine in mastocytosis is reviewed herein.

Keywords

Cladribine, Systemic mastocytosis, Review

the treatment of systemic mastocytosis. Cladribine is a chemotherapeutic compound that can be administered intravenously or subcutaneously. It is a prodrug that is activated after uptake in cells [4]. Their function as an antimetabolite that induces DNA strand breaks and is toxic in hematopoietic cells and leukemic and lymphatic malignancies, but has little or no effect in non-hematopoietic tissues and solid tumors. It is polyvalent and is toxic for dividing and quiescent cells [4]. Cladribine induces myelosuppression and immunosuppression. Cladribine has generally been used after symptomatic therapy and interferon-alpha were not effective. A review of its efficacy in mastocytosis is described herein.

Introduction

Mastocytosis is a heterogenous disease characterized by accumulation of mast cells in one or more organs [1]. The disease may present with skin lesions only (cutaneous mastocytosis, CM) or may be present in other organs (systemic mastocytosis, SM). Cutaneous mastocytosis is divided into maculopapular, diffuse cutaneous mastocytosis and solitary mastocytoma of the skin [1,2]. SM is divided into indolent systemic mastocytosis (ISM), smoldering systemic mastocytosis (SSM), SM associated with clonal non-mast cell lineage disease (SM-AHNMD), aggressive systemic mastocytosis (ASM) and mast cell leukemia (MCL) [1-3].

In SM different therapeutic approaches have been described including treatment with interferon-alpha, cladribine, tyrosine kinase inhibitors, targeted agents and allogeneic transplantation. Cladribine (2-chlorodeoxyadenosine) is a purine analog that was developed in the 1970s. It was first tested in humans in the early 1980s and became a valuable product for

Results of Studies

Table 1 provides an overview of reports of cladribine in systemic mastocytosis.

Barete, et al. [5] reported 68 adult patients with SM. Twenty-eight had ISM, two SSM, 14 ASM, 17 SM-AHNMD, 1 MCL and 6 CM. CM, SSM and ISM were grouped as indolent mastocytosis (36 patients) and ASM, SM-AHNMD and MCL as advanced mastocytosis (32 patients). Cladribine 0.14 mg/kg/d was administered as 2-hour infusion or subcutaneously for five days. Median 3.68 (range 1-9) courses were administered with median 52 (range 28-83) days interval. The overall response rate was 72%; 47% had major response and 25% partial response. In indolent mastocytosis the response rate was 92% (MR 56%, PR 36%) and in advanced mastocytosis 50% (MR 37.5%, PR 12.5%). 43% of patients with ASM responded and 59% of patients with SM-AHNMD. The median number of cladribine courses for all patients was four for responders and three for non-responders. At median 5.8 years follow-



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Table 1: Cladribine in Systemic mastocytosis.

Author	Prior Treatment	Treatment with cladribine	Patients	ORR	PFS/RFS	OS	Comment
Barete S, et al. [5]	INF-alpha, TKIs	0.14 mg/kg/d 2-hour i.v. of s.c. for 5d, median 3.68 cycles.	68 SM	ORR 72%, MR 47%, PR 25%	Median RFS ISM 3.71 y, ASM 2.47y, 4.77 SM-AHNMD	At 5.8 years 92% Median OS 8.2y	Response ISM 92%, ASM 50%
Lim KH, et al. [6]	Unknown	5 mg/m ² or 0.13-0.17 mg/kg/d i.v. for 5d, median 3 cycles.	26 SM, 22 evaluable	ORR 55%, MR 37%	Median 11 (3-74) m		ORR in ISM 56%, ASM 50%, SM-AHNMD 55%
Kluin Nelemans HC, et al. [7]	H1/H2 blocker	0.13 mg/kg/d 2-hour i.v. for 5d, 6 cycles.	10, 3 ASM	ORR 10 (100%) 2 MR, 1 good PR	1 relapse after 6 months		Relapsed pat responded to 2 nd line cladribine.
Pardanani A, et al. [8]	INF-alpha ± hydroxyurea	0.14 mg/kg/d 2-hour i.v. for 5d, 4-5 cycles.	4, ASM	ORR 3 (75%) 2 MR, 1 good PR			
Wimazal F, et al. [9]	H1/H2 blockers, steroids, INF-alpha	0.13 mg/kg/d i.v. for 5 days, 3 and 9 cycles.	2 SSM with anaphylactic episodes.	ORR 2, CR 2	2+, 6+ years		
Tef [Feri A, et al. [10]	RT, H1/H2 blocker, IFN-alpha	0.13 mg/kg/d 2-hour i.v. for 5d, 6 cycles.	1, SM	ORR 1	12+ m		
Escribano L, et al. [11]	CVP INF-alpha	0.15 mg/kg/d 3-hour i.v. for 5d, 5 cycles.	1, lymphoma and bone marrow mastocytosis.	ORR 1			
Schleyer V, et al. [12]	H1/H2 blocker, PUVA, IFN-alpha	0.13 mg/kg/d i.v. for 5d, 7 cycles.	1 SSM	ORR 1			
Penack O, et al. [13]	IFN-alpha	1.1. mg/kg/di.v. for 5d, 6 cycles.	1 MCL	CR 1	PFS 30+ m		
Aichberger KJ, et al. [14]	IFN-alpha	0.13 mg/kg/d iv for 5d, 6 cycles.	1 ASM	ORR 1 after 3 cycles, and progression after 6 cycles.	short	Died from MCL	
Radojkovic M, et al. [15]	H1/H2 blockers	0.15 mg/kg/d i.v. for 5d, 6 cycles.	1 ASM	ORR 1, good PR 1	PFS 10 m		

Lock AD, et al. [16]	Topical steroids, fexofenadine, ranitidine, chromoglycate, PUVA, INF-alpha, Thalidomide, nilotinib	0.13 mg/kg/d i.v. for 5 days, 5 cycles.	1 SM	ORR 1, MR 1	At 4 y only mild pruritus.		
Alstadhaug KB, et al. [17]	None	0.12 mg/kg/d 2-hour i.v. for 5d, 9 cycles.	1 ASM	ORR 1, MR 1 after 5 cycles.	RFS 2 years from instatement of cladribine.	Died 3.5 years after MR was obtained.	Developed PML

ORR = Overall Response; CR = Complete Response; MR = Major Response; PR = Partial Response; PFS = Progression Free Survival; RFS = Relapse Free Survival; OS = Overall Survival; SM = Systemic Mastocytosis; ASM = Aggressive Systemic Mastocytosis; SSM = Smoldering Systemic Mastocytosis; MCL = Mast Cell Leukemia; ISM = Indolent Systemic Mastocytosis; RT = Radiotherapy; IFN = Interferon; PUVA = Psoralen Ultraviolet Radiation; TKI = Tyrosine Kinase Inhibitors; PML = Progressive Multifocal Leukencephalopathy; I.V.= Intravenous; S.C.= Subcutaneous.

up 60% had relapsed and 8% died. The median relapse free survival was 3.71 years for indolent mastocytosis, 2.47 years for ASM and 4.77 years for SM-AHNMD. Median overall survival was 8.2 years were by survival was longer for indolent mastocytosis than for advanced mastocytosis.

Lim, et al. [6] reported 108 patients with SM, 26 had received cladribine as first line therapy. Patients had either ISM (10), ASM (3) or SM-AHNMD (13). Cladribine was administered at a dose of 5 mg/m² or 0.13-0.17 mg/kg/d for 5 days as 2-hour intravenous infusion. The median number of cycles in twenty patients was 3 (range 1-9). Twenty-two patients were evaluable for response. One patient obtains a complete response, seven a major response and four a partial response for an overall response rate of 55%. The overall response rate was 56% in ISM, 50% in ASM and 55% in SM-AHNMD. The median duration of response was 11 (range 3-74) months. Presence of leukocytosis, monocytosis or circulating immature myeloid cells was associated with inferior response.

Kluin Nelemans, et al. [7] reported ten patients, three with ISM, one with SSM, three with ASM and three with SM-AHNMD. Cladribine 0.13 mg/kg/d as 2-hour infusions for five days were administered. Cycles were repeated at 4 to 6-week intervals and nine patients completed six cycles. All patients with aggressive mastocytosis showed a response and all other patients an improvement of signs and symptoms. All seven patients with urticaria pigmentosa showed a reduction of the red-brown maculae from > 50% of skin involvement to almost disappearance. Two patients with bone marrow mastocytosis and atypical chronic myeloid leukemia showed a decrease of leucocytes during treatment with cladribine, but a rapid increase after cessation of the therapy. In most patients a steep decrease of serum tryptases and urinary parameters had

occurred already after the first course of cladribine. All patients responded with improvement of mastocytosis related symptoms. One patient experienced a relapse starting six months after the last cladribine treatment. Cladribine treatment was resumed 3 months later and induced a second response.

Pardanani, et al. [8] reported four patients with ASM resistant to interferon-alpha, who were treated with cladribine 0.14 mg/kg/d as 2-hour infusions for five days for a total of three to six courses administered over a period of 3 to 36 months. One patient had a dramatic response to the first course of cladribine, and after five courses there was complete resolution of all symptoms and skin rash and a dramatic mast cell cyto reduction. The second patient had skin involvement, hepatosplenomegali and bone marrow involvement. After four courses of treatment there was significant improvement in symptoms, skin rash, anemia and liver and spleen size. The third patient initially diagnosed with urticaria pigmentosa and later ASM obtained a major response to four cycles of cladribine. The fourth patient with SM of the skeleton did not respond to three courses of cladribine.

Wimazal, et al. [9] reported two patients with SSM and anaphylactic episodes who did not respond to H1/H2 blockers and steroids. One patient also received interferon-alpha without effect. Cladribine 0.13 mg/kg/day as 2-hour infusion for five days was instated for three and nine courses. Both patients became free of anaphylactic episodes for 6+ and 2+ years respectively.

Tefferi, et al. [10] reported a 57-year-old patient with systemic mastocytosis refractory to subcutaneous interferon-alpha, who received cladribine 0.13 mg/kg/d as 2-hour infusion for 5 days. Six cycles were administered at six months interval. After the fourth cycle skin lesions had completely resolved and the bone marrow showed a marked reduction of mast cell

infiltration. One year after the sixth cycle the patient was free of all manifestations of mastocytosis and the bone marrow only contained minimal residual disease.

Escribino, et al. [11] reported a 65-year-old patient with lympho plasmacytic lymphoma and bone marrow mastocytosis, who's lymphoma responded to cyclophosphamide, vincristine, prednisone [CVP]; concurrently administered interferon-alpha did not induce a response of the bone marrow mastocytosis. Due to progression of the lymphoma cladribine 0.15 mg/kg/d as 3-hour infusion for 5 days was instated. After five cycles an objective clinical response of the lymphoma was obtained. The bone marrow showed small clones of normal and abnormal mast cells. The mast cells consisted of two clones, one expressing the same markers as found at diagnosis and one distinct clone negative for CD2, CD25 and CD35, which was a population of normal mast cells. This suggested that cladribine specifically targets CD25 expressing mast cells and induced a response.

Schleyer, et al. [12] reported a 53-year-old patient, since the age of 37 known with urticaria pigmentosa, who developed an indolent non-Hodgkin lymphoma and bone marrow involvement with mastocytosis was diagnosed. The patient had been treated with H1/H2 blockers, PUVA, cimetidine, chromoglicate, steroids and interferon-alpha. Cladribine 0.13 mg/kg/d i.v. for five days was instated. The patient had a rapid response of skin lesions and after seven courses of cladribine the bone marrow infiltration was no longer progressive.

Penack, et al. [13] reported a 65-year-old patient with MCL. No response to interferon-alpha was observed. Cladribine 0.1 mg/kg/d i.v. for five days was instated. Six courses were administered on time. After the first course mediator related symptoms started to improve and after six courses splenomegaly had decreased, serum tryptase dropped to normal level and bone marrow mast cell infiltration decreased from 90% to 10-15%. Thirty months after treatment the patient was still free of disease.

Aichberger, et al. [14] reported a 71-year-old patient who was diagnosed with ASM. Treatment with H1/H2 blockers, prednisolone and interferon-alpha did not induced stable disease for half a year, where after the disease progressed. Cladribine was instated at a dose of 0.13 mg/kg/d i.v. for 5 days. After the third cycle a major response was obtained. After the sixth cycle a bone marrow aspirate showed 10% mast cell infiltration. Five months later MCL was diagnosed and two more cycles of Cladribine were administered, which did not induce an objective response. Dasatinib treatment was instated without result. The patient died of progressive disease and subarachnoidal bleeding.

Radojkovic, et al. [15] reported a 40-year-old woman initially diagnosed with CM, who developed ASM with

fever, fatigue, anemia, thrombocytopenia, occasional diarrhea, rash and splenomegaly. Cladribine was administered at a dose of 0.15 mg/kg/d for five days during six cycles at 4 weeks interval. A good partial response was obtained with transfusion independence and normalization of spleen size. Relapse was observed after 10 months.

Lock, et al. [16] reported a 62-year-old patient with a 4-year history of a pruritic rash. The patient developed bone marrow mastocytosis and was treated with interferon-alpha, thalidomide and nilotinib without response. Cladribine 0.13 mg/kg/d for 5 days intravenously was administered during five courses at 4 weeks interval. At follow-up four years later the patient only had mild pruritus controlled with loratadine.

Alstadhaug, et al. [17] reported a 67-year-old male who was diagnosed with ASM. Cladribine 0.12 mg/kg/d was administered as 2-hour i.v. infusions for 5 days during nine courses. A major response was obtained after five courses but 2 years after initiation of cladribine relapse was observed. Five months after the last course of cladribine he was diagnosed with progressive multifocal leukoencephalopathy and died three weeks after the request that all life extending treatment including nutrition was stopped.

Discussion

Disease responses in mastocytosis are defined for cutaneous, symptomatic and aggressive forms of disease and can for ASM and MCL be described as complete (100% regression), major (complete resolution of at least one type of mastocytosis-related organ damage (C-findings) and no progression of other C-Findings), good partial [$\geq 50\%$ regression), minor ($< 50\%$ regression) or no response (stable or progressive disease) [18]. Cladribine induced complete responses in cutaneous manifestation and major or partial responses in indolent and aggressive forms of systemic mastocytosis [5-17]. None of the reports described the use of cladribine solely for cutaneous lesions but patients with cutaneous and systemic involvement, obtained complete resolution of skin manifestations while complete or major response of systemic lesions were reported [9,10,12,16]. One report described a patient with MCL who obtained a complete response [10]. In publications that reported more than one patient the overall response rate varied from 55% to 100% [5-9]. In the single patient reports the duration of response varied from months to years [10,13-17]. Although Lim, et al. reported a median progression free survival of 11 months in twenty-two patients with systemic mastocytosis, Barete, et al. reported median relapse free survival of 3.71 years for ISM, 4.77 years for SM-AHNMD and 2.47 years for ASM in sixty eight patients [5,6]. Kluijn Nelemans, et al. reported only one relapse in ten patients, responding again to cladribine upon retreatment [7].

Barete, et al. is the only author who reported subcutaneous use of cladribine [5]. Intravenous and subcutaneous cladribine have been reported to be equally efficient [19,20].

In several publications cladribine was administered after failure of interferon-alpha or tyrosine kinase inhibitors [5,8-14,16].

Other Treatment of SM

The guidelines recommend midostaurin, cladribine, imatinib, interferon plus or minus steroids or allogeneic transplantation for treatment of advanced systemic mastocytosis, which encompasses ASM, SM-AHNMD and MCL [21]. Midostaurin is registered for systemic mastocytosis based on an open label study that examined its use in ASM, SM-AHNMD and MCL [22]. Eighty-nine patients were evaluable for response sixteen with ASM, fifty-seven with SM-AHNMD and sixteen with MCL [22]. The overall response rate was 60% with 45% major responses. The response rates for ASM/SM-AHNMD/MCL were 75%, 58% and 50% respectively. Median progression free survival was 28.7 months, 11 months and 11.3 months respectively and overall survival was not reached at 26 months, 20.7 months, and 9.4 months respectively. In another study in twenty-six patients who received midostaurin for twelve cycles an overall response rate of 69% (50% major response) was reported in three patients with ASM, seventeen patients with SM-AHNMD and 6 patients with MCL [23]. Comparable results for cladribine reported by Kluin Nelemans, et al. were 100% overall response in three patients with ASM and improvement of signs and symptoms not further specified in three patients with SM-AHNMD [7]. Lim, et al. reported for cladribine 50% overall response in two patients with ASM and 55% overall response in eleven patients with SM-AHNMD [6]. Barete, et al. reported for cladribine 43% overall response in fourteen patients with ASM and 59% response in seventeen patients with SM-AHNMD [5]. Interferon-alpha induced seven partial responses and six minor responses in thirteen of twenty evaluable patients with bone marrow involvement [24]; the responses were observed in vascular congestion and skin lesions but not in the bone marrow. In another small serie of five patients with ASM two major responses and one partial response were observed with interferon-alpha [25]. Imatinib has shown activity in KIT negative systemic mastocytosis [26-28]. In twenty patients with systemic mastocytosis imatinib induced one complete response and six patients showed symptom improvement [27]. In another series of ten patients with KIT negative mastocytosis, three with cutaneous mastocytosis, three with ISM, three with MCL and one with SM-AHNMD, an overall response of 50% was reported; two of the responders had advanced mastocytosis [28]. Nilotinib, another tyrosine kinase inhibitor, was reported to induce a response of 21.6% in thirty-seven patients with ASM, eight of whom were KIT positive [29].

Thus, midostaurin and cladribine induce most favorable responses in advanced mastocytosis, but alpha-interferon and in KIT negative patients imatinib may be best alternatives.

Conclusion

Cladribine is one of the most efficient compounds in systemic mastocytosis and can be considered a valuable treatment option [5-7,9,13].

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