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Cladribine in the Treatment of Waldenström Macroglobulinemia, Where Do We Stand?

Marlies Van Hoef*

Van Hoef Consulting

***Corresponding author:** Marlies Van Hoef, MD, PhD, MBA, Van Hoef Consulting, Email: vanhoef@vanhoefconsulting.com

Abstract

Waldenström macroglobulemia is a rare disease for which treatment with cladribine (2-chorodeoxyadenosine) has been reported since 1993. Cladribine has meanwhile been administered to several hundreds of reported patients either as monotherapy or in combination therapy and is available for intravenous and subcutaneous administration. Cladribine has been used in treatment naive and previously pretreated patients. Literature describing the use of cladribine, combinations of other medications and ibrutinib in Waldenstrom's Macroglobulinemia is reviewed herein.

Key words: Waldenström macroglobulinemia; Cladribine; Combination treatment; Ibrutinib review

Introduction

Waldenström Macroglobulinemia (WM) is a rare indolent B-cell lymphoproliferative disorder characterized by the accumulation of monoclonal cells in the bone marrow and peripheral lymphoid tissues, and associated with the production of serum immunoglobulin M (IgM) monoclonal protein. The age-adjusted annual incidence rate is 3.4 per million in men and 1.7 per million in women in the United States and 7.3 and 4.2 per million respectively in Europe[1,2]. The disease accounts for approximately 1% to 2% of non-Hodgkin lymphomas. The main clinical symptoms arecytopenia, hyperviscosity syndrome, epistaxis, constitutional symptoms, lymphadenopathy and hepatosplenomegali. The diagnosis is confirmed by the presence of IgM monoclonal protein in the serum and a bone marrow biopsy showing > 10% clonal lymphoplasmacytic cells. Cladribine (2-chlorodeoxyadenosine) is a purine nucleoside analog that was developed in the 1970s. It was first tested in humans in the early 1980s. Cladribine is a chemotherapeutic compound that can be administered intravenously or subcutaneously. It is a prodrug that is activated after uptake in cells[3]. It functions as an antimetabolite 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[3]. Cladribine induces myelosuppression and immunosuppression. A review of its efficacy in WM is described in this paper.

Review

Table 1 displays studies with cladribine for symptomatic WM that have been reported chronologically over time.

In the initial reports cladribine was administered as monotherapy for two to five cycles intravenously and up to six cycles subcutaneously[4-16]. In studies at later date cladribine was administered in combination treatment[17,18]. Cladribine two to four cycles induced overall response rates from 85% to 100% in treatment naïve patients[4-17]. Among responders were complete response[9-18]. Overall response rates were lower in studies that combined treatment naive and pretreated patients and varied from 28.6% to 89.6%[4-18]. The variation may depend on number of prior treatments and the percentage of untreated patients in the cohort. Dimopoulos et al. found an overall response rate of 92% to 100% in untreated and 40% to 48% in pretreated patients with two cycles of cladribine[4,5]. In a study reporting cladribine, with cladribine plus prednisone, cladribine plus cyclophosphamide, or cladribine plus cyclophosphamide plus rituximab in treatment naïve patients, response rates with two cycles of cladribine monotherapy (94%) were comparable with those with the two

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Table 1: Cladribine in patients with WM

Author	Pretreatment	Treatment	Patients	ORR	PFS	OS	Commend
4)Dimopoulos MA	Pretreated 20 Untreated 9	Cladribineiv 2 cycles	29, median age 65y	ORR 17 (59%) 100% untreated 40% pretreated	At 7m follow-up 1 responding pat had relapsed	At 7m OS 89.7%	
5)Dimopoulos MA	Pretreated 53 Untreated 15	Fludarabine (28) Cladribine iv (40) median 5 cycles	68	ORR 35 (51.5%) 4 CR ORR cladribine untreated 92% pretreated 48%	At 18m follow-up in untreated pat 86.7%. Med DOR in pretreated pat 38m.	At 18m OS in untreated pat 100%. Med OS in pretreated pat 43m.	At analysis 2 of 15 untreated patients had relapsed
6)Zaucha JM	Untreated 1	Cladribine iv	1, aged 68y	ORR 1 (100%) 1 PR			
7)Dimopoulos MA	Pretreated Fludarabine 14	Cladribine iv 2 cycles	14	ORR 4 (28.6%) 4 PR			
8)Delannoy A	Pretreated 13 Untreated 5	Cladribine iv median 2 cycles	18, median age 69y	ORR 7 (38.8%) 7 PR			
9)Dimopoulos MA	Untreated 26	Cladribine iv 2 cycles	26	ORR 22 (85%) 3 CR, 19 PR	At 13m follow-up 5 pat had relapsed	At 13m OS 81%	Pat retreated after relapse had again response
10)Dimopoulos MA	Pretreated 46	Cladribine iv 2 cycles	46	ORR 20 (43%)	Median 12 months	Median 28 months	Response dependent on disease state
11)Richards AI, J	Untreated 1	Cladribine iv 4 cycles	1, meningeal involvement	1 CR (100%)	DFS 15+ m		
12)Fridrik MA	Untreated 10	Cladribine iv 4 cycles	10, median age 62.3y	ORR 100%, 1 CR, 8 PR, 1 MR	At median 57w 70%	At median 57w 90%	
13)Betticher DC	Pretreated except for 1 pat	Cladribinesc max 6 cycles	25, median age 65y	ORR 68% incl. dis. Stabilization 10 PR (40%)	Med DOR 8m		
14)Liu ES	Untreated 7 Pretreated 18	Cladribine iv 3 cycles with continuation if PR achieved	20, median age 66y	ORR 55%, 1 CR, 10 PR		At 20 m 85%	57% untreated and 54% pretreated responded
15)Hellmann A	Untreated 9 Pretreated 13	Cladribine iv 4 cycles	22, median age 62y	ORR 41% 1 CR, 8 PR, 10 stabilization	Mean DOR in responders 12m		Response 38% in pretreated, 44% in untreated
16)Lewandowski	Untreated 11 Pretreated 14	Cladribine iv, mean 3 cycles	25, mean age 63y	ORR 64% 1 CR, 15 PR			Six patients obtained stable disease
17)Weber DM	Untreated 94	Cladribine iv vs Clad iv + Pred vs Clad sc + Cyclo vs Clad sc + CycloRitux 2 cycles	16, med age 67y 20, med age 61y 17, med age 62y 9, med age 63y	ORR 94%, 3 CR ORR 60%, 1 CR ORR 84%, 2 CR ORR 94%, 3, CR	Med DOR 23 m Med DOR 9 m Med DOR 36 m DOR NR at med 21m	Median 73 m Median 41 m Not reached Not reached	2nd line ORR 80% 2nd line ORR 88% 2nd line ORR 77%
18)Laszlo D	Untreated 16 Pretreated 13	Cladribinesc +Rituximab 4 cycles	29, median age 64y	ORR 89.6%, 7CR, 16 PR, 3 MR	At 43m FU 4 patients relapsed		No difference in response pretreated and untreated

ORR=overall response rate, PFS=progression free survival, DFS=disease free survival, OS=overall survival, CR=complete response, PR=partial response, MR=minor response, DOR=duration of response, iv=intravenous, sc=subcutaneous, Clad= cladribine, Pred= prednisone, Cyclo= cyclophosphamide, CycloRitux= cyclophosphamide, rituximab, m=months, FU=follow-up

latter combinations (84% and 94%) respectively and higher than those when cladribine was combined with prednisone (60%)[17]. In this study retreatment with cladribine in second line resulted in response rates of 77% to 88%. Successful retreatment after relapse had already previously been reported[9]. Duration of response and progression free survival was longer for treatment naive than for pretreated patients. In treatment naïve patients response duration was in general longer when cladribine was used in combination than when cladribine was used as monotherapy, but the number of cycles administered may also have influenced the response duration . Weber et al. reported median response durations of 23 months, 9 months, 36 months and not reached at median 21 months with respectively cladribine, cladribine plus prednisone, cladribine plus cyclophosphamide and cladribine plus cyclophosphamide plus rituximab in treatment naïve patients who received two cycles[17]. Ten of fifteen patients responding to cladribine, eight of twelve responding to cladribine and prednisone, and thirteen of thirty one responding to cladribine plus cyclophosphamide were retreated with the same therapy after relapse[17]. The duration of second remission was similar to the first remission, being 24, 14 and 30 months respectively. Laszlo et al. reported a response rate of 79.7% in treatment naïve and pretreated patients who received subcutaneous cladribine and rituximab[18]. At 43 months follow-up relapse free survival was 84.6 % in patients who had responded to four cycles of the combination of cladribine and rituximab. Durations of response or progression free survival in studies with cladribine monotherapy including treatment naïve and pretreated patients were shorter than in studies including treatment naïve patients only, Cladribine was in general administered intravenously but subcutaneous administration was also reported . In the various studies cladribine intravenously was given at a dose of 0.1 mg/kg/d continuously for 7 days or at a dose of 0.12 to 0.14 mg / kg / d or 4 to 5.6 mg/m2/d over two hours for five days. Subcutaneous injection occurred at a dose of 0.1 mg / kg / d for five days either as monotherapy or in combination therapy. Subcutaneous and intravenous administration are equally efficient but subcutaneous administration is more convenient and cost-saving[19,20].

Various treatments for WM other than cladribine have been reported in studies that included patients with treatment naïve symptomatic WM:

Table 2 displays regimens that have been reported in treatment naïve patients. Dexamethasone plus rituximab plus cyclophosphamide induced overall response rates of 83% to 96% in treatment naïve patients[21-23]. Median progression free survival exceeded two years and was 34 to 35 months[21-23]. Castillo et al. reported three different combination treatments including rituximab and rituximab maintenance and observed a major response rate of 97% in treatment naïve patients compared to 68% in patients who received no maintenance[24]. Progression free survival was median 6.8 years with and 2.8 years without rituximab maintenance and overall survival 84% with and 66% without rituximab maintenance[24]. Half-dose cyclophosphamide, doxorubine, vincristine, prednisone plus rituximab (CHOP-R) induced an overall response of 65% and a progression free survival at two years of 70% in treatment naïve patients[25]. Three bortezomib plus rituximab containing treatment regimens induced overall response rates of 85% to 96% in treatment naïve patients[26-28]. This combination resulted in an event free survival of 79% at one year[28]; when dexamethasone was added median progression free survival was 42 months and with rituximab maintenance progression free survival at 22.8 months was 78.3 % (26,28). Carfilzomib, rituximab plus dexamethasone with same maintenance regimen resulted in 87.1% overall response rate, and at 15.4 months progression free survival in 64.5% of patients naive to bortezomib and rituximab[29]. Ibrutinib induced 100 % overall response in 30 treatment naïve patients[30]. At 14.6 months follow-up 6.7 % of patients had relapsed. The effect of continuous (maintenance) treatment with ibrutinib became apparent in a study reported by Gustine at al., who reported an IgM rebound 4 weeks after discontinuation of ibrutinib[31].

Various treatments for WM other than cladribine have been reported in studies that included symptomatic treatment naïve and relapsed and / or refractory patients:

Table 3 displays regimens that have been reported in such studies. Cyclophosphamide and fludarabine for four cycles induced overall response rates of 55% to 76% with a median progression free survival of 24 months and median duration of response of 38 months in treatment naïve and pretreated patients[32,33]. The overall response rate with four fludarabine based combinations was 90% and median progression free survival 43.1 months[34]. Fludarabine, cyclophosphamide plus rituximab for at least four cycles induced an overall response of 79% to 85.4% and at median 47 to 51 months median progression free survival was not reached[35-37]. In one report median event free survival was 77 months[36]. Pentostatin combined with cyclophosphamide with or without rituximab induced an overall response of 64.7% and maintenance rituximab prevented relapse in 58.8% of treatment naïve and pretreated patients[38]. The same regimen induced two years progression free survival in 83.7% and when this regimen was in addition used as maintenance the progression free survival increased to 91.7%[39]. Bendamustine plus rituximab induced response rates from 80.2% to 95% in pretreated patients[40-42]. Median progression free survival varied from 13.2 months to 58 months[40-42]. Dexamethasone, rituximab plus cyclophosphamide induced an overall response of 87% in treatment naïve and pretreated patients[24,43]. Median progression free survival was 32 months[23,42]. Cyclophamide, doxorubicine, vincristine, prednisone plus rituximab with rituximab maintenance in part of the patients induced a high overall response of 92.3% in treatment naïve and relapsed and refractory patients and at 9 months a progression free survival of 76.9%[43]. Two bortezomib plus rituximab based combination treatments induced an overall response of 81% and 89% in pretreated patients[44,45]. The median time to progression and was 15.6 months and the median progression free survival 21 months respectively[44,45]. Bortezomib monotherapy or bortezomib plus prednisone though induced lower response of 43.2% in advanced WM[46]. Dimopoulos et al. reported an overall response of 90%, with 71% major response with ibrutinib in rituximab refractory patients, who had received median four prior cycles[47]. Median progression free survival at 18 months was 86%. In another study including treatment naïve and pretreated patients ibrutinib plus rituximab induced an overall response of 92% with 72% major response[48].

Ibrutinib was administered continuously and at 30 months progression free survival was 82%[48].

Table 2: Studies with other medications that included treatment naive WM patients

Author	Pretreatment	Treatment	Patients	ORR	PFS/DFS	OS	Commend
21.Dimopoulos MA	untreated	DexaRituxCyclo 8 cycles	72	ORR 83% 7% CR, 67% PR, 9% MR	2y PFS 67% and for responders 80%	2y OS 90%	Median time to response 4.1m
22.Kastritis E	untreated	DexaRituxCyclo at 7y FU, retreatment upon relapse	72	ORR 83% 7% CR, 67% PR, 9% MR	Med PFS 35m	8y OS 64% 10y estimated OS 53%	Med PFS rituxalone 23m, rituxcombination 3y
23.Paludo J	50 untreated 50 rel/ref	DexaRituxCyclo	100	ORR 87% Untreated ORR 96%	Med PFS 32m Untreated med PFS 34m		Med TTNT 50m Untreated med TTNT NR
24.Castillo JJ	Untreated	DexaRituxCyclo DexaBortezoRituxBendaRitux maintenance Rituxvs no maintenance	38 87 57 116	Med TTBR 30m Med TTBR 20m Med TTBR 18m Major R 97% vs 68%	Med PFS 4.8y Med PFS 5.8y Med PFS 5.5y Med PFS 6.8y vs 2.8y	10y OS 81% 10y OS 96% 10y OS 95% 10y OS 84% vs 66%	Maintenance added ORR, PFS and OS
25.Sekiguchi N	Untreated	½ dose CHOP-R 6 cycles	20	ORR 13 (65%)	2y PFS 70%	2y OS 93.3%	
26.Treon SP	Untreated	DexaBortezoRitux 4 cycles induction, 4 cycles mainten	23	ORR 96%, Major R 83%, 3 CR	At 22.8m PFS 78.3%		Responses after 1.4 months
27.Ghobrial IM	Untreated	BortezoRitux 4 cycles, Rituxin cycles 1 and 4	26	ORR 88% 1CR, 1 nCR, 15 PR, 6 MR	1y EFS 79%		
28.Dimopoulos MA	Untreated	DexaBortezoRitux 5 cycles, with DexaRituxin c 2+5	59	ORR 85%, 3% CR, 7% VGPR 58% PR	Med PFS 42m 3y DOR 70%	3y OS 81%	Peripheral neuropathy in 46%
29.Treon SP	Naïve to Bortezo + Ritux	CarfilzoRituxDexa Maintenance same mainten 8 cycles	31	ORR 87.1% 1 CR, 10 VGPR, 10 PR, 6 MR	At 15.4m 20 pat progression free		
30.Treon SP	Untreated	Ibrutinib	30	ORR 100%, Major R 83%	At 14.6 m FU, 2 pat progressed Estimated 18m PFS 92%		Wild type CXCR4 vs CXCR4 major r 94% vs 71%, VGPR 31% vs 7%
31.Gustine JN	Discontinuation of ibrutinib	Ibrutinib	189 51 discontinue	IgM rebound 4 wk after discon in 73%; ORR to salvage 71%		OS shorter if progressive on ibrutinib	Discontinuation at 12,24,36,48m 22%, 26%, 35%, 43%

ORR=overall response, PFS=progression free survival, DFS=disease free survival, EFS=event free survival, OS=overall survival, CR=complete response, nCR=near complete response, VGPR=very good partial response, PR=partial response, MR=minor response, major r=major response, DOR=duration of response, TTBR=time to best response, med=median, m=months, y=year, TTNT=time to new treatment, NR=not reached, FU=follow=up, rel/ref=relapsed/refractory, DexaRituxCyclo= dexamethasone, rituximab, cyclophosphamide, DexaBortezoRitux= dexamethasone, bortezomib, rituximab, BendaRitux= bendamustin, rituximab, CHOP-R= cyclophosphamide, doxorubicin, vincristine, prednisone, rituximab, CarfilzoRitux,Dexa =carfilzomib, rituximab, dexamethason

Table 3: Studies with other medications that included treatment naive and pretreated patients with WM

Author	Pretreatment	Treatment	Patients	ORR	PFS/DFS	OS	Commend
32.Dimopoulos MA	7 refractory 2 relapsed 2 untreated	FludaCyclo 4 cycles	11, median age 73y	PR 6 (55%)	Med PFS 24m		At 28m FU, 2 of 6 responders progressed
33.Tam CS	4 untreated 14 pretreated	FludaCyclo 4 cycles	18	PR 13 (76%)	Med DOR 38m	At 37m for untreated pat 100% 5y OS pretrea-ted pat 55%	
34.Peinert S	10 untreated 19 pretreated	FludaCyclo FludaCycloRitux FludaMitox FludaRitux	29	ORR 26 (90%) 1 CR, 23 PR, 2 MR	Med PFS 43.1m	5y OS 88% 10y OS 75%	Untreated patients all responded and alive at med 50m
35.Tedeschi A	Untreated Pretreated	FludaCycloRitux 6 cycles	43	ORR 79% Major response 74.4%			After FU continuation improvement leading to 18.6% CR
36.Tedeschi A	Untreated Pretreated	FludaCycloRitux	40	ORR 32 (80%) VGPR 32.5%	Med EFS 77m At med 51m FU, med PFS NR		
37.Souchet L	25 untreated 57 pretreated	FludaCycloRitux 5 cycles	82, MED AGE 61y	ORR 85.4%	At med FU 47m, med PFS NR 48m PFS 67%	3y OS 90%	Best response at 10.8 months major resp from 64.6% to 76.8%
38.Hensel M	9 untreated 8 pretreated	PentostCyclo+Ritux + maintenance ritux 4-6 cycles	17	ORR 11 (64.7%) 2 CR, 9 PR	Maintenance rituximab prevented relapse in 10 pat		In pat who received rituximab ORR 76.9%
39.Herth	21 untreated 4 pretreated	PentostCycloRitux	25		1st line 2y PFS 83.6%, same for maintenance 91.7%	1st line 2y OS 100%. Same for maintenance 100%	13 pat had rituximab maintenance
40.Treon SP	Rel/ref	BendaRitux Benda +ofatum 5 cycles	30	ORR 25 (83.3%) 5 VGPR, 20 PR	Med PFS 13.2m		
41.Tedeschi A	Rel/ref Median 2 lines of treatment	BendaRitux	71, med age 72y	ORR 80.2% Major response 74.6%	At med 19 m med PFS NR		
42.Paludo J	43 rel/ref 50 rel/ref	BendaRitux DexaRituxCyclo	60 100	Naïve ORR 93% vs 96% Rel/ref ORR 95% vs 87%	Naïve 2y PFS 88% vs 61% Rel/ref med PFS 58 vs 32m	Med OS NR vs 166m	
23.Paludo J	50 untreated 50 rel/ref	DexaRituxCyclo	100	ORR 87% Untreated ORR 96%	Med PFS 32m Untreated med PFS 34m		Med TTNT 50m Untreated med TTNT NR
43.Treon SP	3 untreated 3 rel/ 7 ref	CHOP-R 6 cycles 3 pat maintenance Ritux	13	ORR 12 (92.3%) 3 CR, 8 PR, 1 MR	At 9 m PFS 10 of 13 (76.9%)		
44.Ghobrial IM	Pretreated at least one prior therapy	BortezoRitux 4 cycles, Ritux in cycles 1 and 4	37	ORR 81% 2 CR, 17 PR, 11 MR	Med time to progression 15.6m 12m PFS 57% 18m PFS 45%		
45.Ghobrial IM	Rel/ref	EverolRitux EverolBortezoRitux maintenanceEverol 6 cycles	10 36	ORR in 36 89% 2CR, >PR 19 (53%)	Med PFS 21m		
46.Leblond V	Advanced WM	Bortezo; in non-res-ponding patients dexa after 2nd cycle 6 cycles	34	ORR after 2 cycles 43.2%	Med PFS 15.3m		
47.Dimopoulos MA	Ritux refractory Median 4 prior therapies	Ibrutinib	31, medianage 67y	At med 18.1m ORR 90%, 71% major resp	18m PFS 86%	18m OS 97%	Time to 1st response 1m
48.Dimopoulos MA	Untreated 45% Pretreated 55%	IbrutinibRitux vs PlaceboRitux	150	ORR 92% vs 47% major response 72% vs 32% VGPR 23% vs 4%	At 30m PFS 82% vs 28%	At 30m OS 94% vs 92%	At 24m in pat with major resp DOR 92% vs 41%

ORR=overall response, PFS=progression free survival, DFS=disease free survival, OS=overall survival, CR=complete response, VGPR=very good partial response, PR=partial response, MR=minor response, DOR=duration of response, NR=not reached, TTNT=time to next treatment, FU=follow-up, rel/ref=relapsed/ refractory, FludaCyclo= fludarabine, cyclophosphamide, FludaCycloRitux= fludarabine, cyclophosposphamide, rituximab, FludaMitox= fludarabine, mitoxantrone, PentostClyco= pentostatin, cyclophosphamide, BendaRitux= bendamustine, rituximab, DexaRituxCyclo= dexamethasone, rituximab, cyclophosphamide, CHOP-R= cyclophosphamide, doxorubicin, vincristine, prednisone, rituximab, BortezoRitux= bortezomib, rituximab, EverolRitux= everolimus, rituximab

Discussion

Comparing the response rates of two to four cycles cladribine monotherapy subcutaneous or intravenous in treatment naïve patients (85% to 100%) with those of other combination regimens of which at least four cycles were administered (dexamethasone, rituximab, cyclophosphamide 83% to 96%[21,23] triple combinations with or without rituximab maintenance 97% vs 68%[24], cyclophosphamide, doxorubicin, vincristine, prednisone, rituximab 65%[25], dexamethasone, bortezomib, rituximab with or without maintenance 96% vs. 85%[26,28], dexamethasone, bortezomib, rituximab 85% to 88%[27,28], dexamethasone, carfilzomib, rituximab with maintenance 87.1%[29] and ibrutinib 100%[30]), cladribine monotherapy induced high response rates and good durations of response. Compared to ibrutinib, it needs to be considered that ibrutinib has to be taken continuously, and that an IgM rebound occurs after discontinuation whereas only two to four cycles of cladribine are required to induce 85% to 100% overall response for a median duration of 23 months in treatment naïve patients . Thus cladribine, which can be administered subcutaneously, is a cost-saving treatment in situations in which ibrutinib is not available, or costs of ibrutinib treatment prevent the use, Cladribine monotherapy was moderately efficient in studies in which treatment naïve and pretreated patients were combined (28.6% to 68%). However, the combination of subcutaneous cladribine plus rituximab for four cycles induced an overall response of 89.6 % in treatment naïve and pretreated patients, and at 43 months follow-up only four of twenty six patients had relapsed for a relapse free survival of 84.6%[18]. With other combinations in studies in which treatment naïve and pretreated patients were combined response rates were as following: fludarabine, cyclophosphamide 55% to 76%[32,33], fludrabine, cyclophosphamide, rituximab 79% to 90%[34-37] pentostatine, cyclophosphamide with or without rituximab 64.7%[38], bendamustine, rituximab with or without cyclophosphamide 87% vs. 80.2%[23,40-42], cyclophosphamide, doxorubine, vincristine, prednisone, rituximab and rituximab maintenance 92.3%[43], bortezomib combinations 81% to 89%[44], bortezomib monotherapy 43.2%[46], ibrutibinib 90%[47] and ibrutinib,rituximab 92%[48]. Thus the cladribine with rituximab combination induced overall response rates that were comparable with other combinations[18]. Also in this setting cladribine with rituximab would be a good alternative in case ibrutinib is not available or costs of ibrutrinib treatment prevent the use.

Conclusion

Cladribine monotherapy is an efficient treatment in treatment naïve symptomatic WM and two to four cycles intravenous or subcutaneous cladribine induced high response rates. Cladribine in combination with other drugs is also efficient in treatment naïve patients. Cladribine monotherapy is moderately efficient in cohorts in which treatment naïve and pretreated patients are combined and analyzed jointly. The combination of subcutaneous cladribine plus rituximab is though highly efficient in this setting. In the era of combination treatment and new drugs the results with cladribine indicate that its use should be considered in the treatment of treatment naïve and pretreated patients.

Declaration

The author is consultant to Lipomed AG.

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