Management of noninfectious mixed cryoglobulinemia vasculitis: data from 242 cases included in the CryoVas survey

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Data on the clinical spectrum and therapeutic management of noninfectious mixed cryoglobulinemia vasculitis (CryoVas) in the era of hepatitis C virus screening are lacking. We analyzed data from 242 patients with noninfectious mixed CryoVas included in the French multicenter CryoVas survey. Baseline manifestations were purpura (75%), peripheral neuropathy (52%), arthralgia or arthritis (44%), glomerulonephritis (35%), cutaneous ulcers (16%), and cutaneous necrosis (14%). A connective tissue disease was diagnosed in 30% and B-cell non-Hodgkin lymphoma in 22%, whereas the CryoVas was considered to be essential in 48%. With the use of Cox-marginal structural models, rituximab plus corticosteroids showed the greater therapeutic efficacy compared with corticosteroids alone and alkylating agents plus corticosteroids to achieve complete clinical, renal, and immunologic responses and a prednisone dosage < 10 mg/d at 6 months. However, this regimen was also associated with severe infections, particularly when high doses of corticosteroids were used, whereas death rates did not differ between the therapeutic regimens. The role of each of these strategies remains to be defined in well-designed randomized controlled trials. (*Blood*. 2012; 119(25):5996-6004)

Introduction

Cryoglobulinemia is defined as the presence of circulating immunoglobulins that precipitate with cold temperature and dissolve with rewarming and is sorted according to the classification by Brouet et al.[1] Type I cryoglobulins are associated with lymphoproliferative disorders, whereas mixed cryoglobulinemia (MC; type II and III) is associated with connective tissue diseases, lymphoproliferative disorders, and chronic infections. When MC is found in the absence of well-defined disease, the syndrome is designated as "essential MC." Since the discovery of hepatitis C virus (HCV) infection in 1989, it has become clear that HCV is associated with most cases of MC. Among patients with MC, 60%-90% are infected with HCV.[2-5] Cryoglobulinemia may be responsible for a systemic vasculitis (CryoVas), with manifestations that range from MC syndrome (purpura, arthralgia, and asthenia) to more serious lesions with skin, neurologic, and renal involvement.[6] In patients with HCV infection, the combination of PEGylated IFN-α with ribavirin is the current standard of care for patients with mild-to-moderate disease activity, whereas more aggressive treatment is needed in patients presenting with severe disease.[7,8]

Data on the presentation, the efficacy, and the safety of treatments in noninfectious mixed CryoVas in the era of HCV screening are lacking. The management of noninfectious CryoVas has yet to be defined, although it is traditionally based on a combination of corticosteroids and immunosuppressants or plasmapheresis. The efficacy of these treatments is often disappointing.[9] More recently, limited data on the efficacy and safety of rituximab in noninfectious CryoVas have emerged, suggesting its interest in such patients.[10]

A survey was initiated in France in 2010 to better define the clinical spectrum and the efficacy and safety of treatments of noninfectious mixed CryoVas. Data from the 242 cases of CryoVas included in this survey are reported here.

Methods

Patients

This retrospective survey was conducted in French university and general hospitals in the departments of internal medicine, hematology, nephrology,

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Table 1. Main characteristics of the 242 patients with noninfectious mixed CryoVas included in the survey, according to the type of MC

Characteristics	All patients (n = 242)	Type II CryoVas (n = 203)	Type III CryoVas (n = 27)	*P*
Epidemiologic features				
Age at diagnosis, y, mean ± SD	62.6 ± 14.5	63.2 ± 14.5	60.4 ± 14.9	.36
Female sex, n (%)	163 (69)	136 (69)	20 (74)	.66
Causes, n (%)				.36
Essential MC	117 (48)	95 (47)	15 (56)	
Connective tissue disease	73 (30)	61 (30)	9 (33)	
Hematologic disease	52 (22)	47 (23)	3 (11)	
Clinical manifestations, n (%)				
Skin	201 (83)	172 (85)	19 (70)	.10
Purpura	182 (75)	158 (78)	15 (56)	.02
Acrocyanosis	64 (26)	52 (26)	9 (33)	.49
Ulcers	39 (16)	32 (16)	6 (22)	.41
Necrosis	35 (14)	28 (14)	5 (19)	.56
Peripheral nerve	125 (52)	114 (56)	6 (22)	.001
Sensory	50 (21)	46 (23)	1 (3)	.02
Sensorimotor	75 (31)	68 (33)	5 (19)	.13
Joints	97 (40)	84 (41)	8 (30)	.30
Arthralgias	72 (30)	61 (30)	7 (27)	.82
Arthritis	25 (10)	23 (11)	1 (3)	.32
Kidney	84 (35)	77 (38)	4 (15)	.02
Gastrointestinal tract	13 (5)	12 (6)	0 (0)	.37
CNS	5 (2)	3 (1)	2 (7)	.11
Pulmonary	5 (2)	4 (2)	1 (3)	.47
Biologic features				
Cryoglobulin level, g/L, mean ± SD	0.94 ± 1.61	1.01 ± 1.69	0.42 ± 0.54	.05
C3 level, g/L (0.80-1.40), mean ± SD	0.86 ± 0.31	0.83 ± 0.31	1.07 ± 0.33	.009
C4 level, g/L (0.14-0.40), mean ± SD	0.07 ± 0.09	0.06 ± 0.07	0.16 ± 0.11	< .0001
Creatinine level, μmol/L (55-105), mean ± SD	113 ± 90	112 ± 77	115 ± 136	.86
GFR, mL/min, mean ± SD*	69 ± 31	67 ± 30	78 ± 31	.03
GFR < 60 mL/min, n (%)*	93 (38)	86 (42)	5 (19)	.02
Outcome				
Follow-up, mo, mean ± SD	51 ± 54	52 ± 52	40 ± 46	.28
Serious infections, n (%)	54 (22)	51 (25)	2 (7)	.05
Death, n (%)	42 (17)	40 (20)	1 (4)	.06

For 12 patients, cryoglobulinemia was not typed. Normal values are indicated for C3, C4, and creatinine levels between parentheses. Type II is MC with a monoclonal component. Type III is MC with only polyclonal immunoglobulins.

*GFR was assessed with the Modified Diet in Renal Disease equation.

neurology, dermatology, and rheumatology. The study was performed in accordance with the ethical standards of the Helsinki Declaration, and it was approved by institutional review board. The inclusion criteria for the study were (1) type II or type III MC after detection and immunochemical typing, (2) systemic vasculitis, and (3) diagnosis of CryoVas between January 1995 and July 2010. The exclusion criteria were the presence of anti-HCV and anti-HIV Abs and hepatitis B surface Ag. Although few studies suggested the existence of "occult" HCV and hepatitis B virus infection,[11,12] the demonstration of HCV-RNA and hepatitis B virus–DNA in ultracentrifuged serum, PBMC samples or liver biopsy specimens were not available. A review performed in 2009 by Welker and Zeuzem[13] confirmed our data[14] and those of 2 other studies that used sensitive assays and liver/PBMC assessment, reinforcing the absence of evidence of occult HCV infection.

Patients were considered to have systemic vasculitis if they had, in association with clinical manifestations of vasculitis (purpura, cutaneous ulcers or necrosis, arthralgia or arthritis, myalgia, peripheral neuropathy, renal involvement, cerebral vasculitis, and gastrointestinal involvement), the following: 91) histologically proven vasculitis (n = 174) and/or (2) detectable cryoglobulinemia with at least purpura or cutaneous ulcers as a clinical manifestation in the absence of histology (n = 68). Patients without histologically proven vasculitis but with purpura or cutaneous ulcers and detectable MC were considered to have small-vessel vasculitis on the basis of previously defined clinical and biologic criteria.[6,15] Twelve patients with nontyped cryoglobulinemia were considered to have MC in the absence of a serum monoclonal component. Finally, of the 324 patients included in the CryoVas survey, 242 patients with noninfectious mixed CryoVas from 81 centers were included (see Figure 1).

Clinical and biologic data were recorded for each patient at the time of the initial evaluation, during follow-up, and at the end of follow-up, by the practitioners in charge of the patients with the use of a standardized form. Laboratory assessment included the determination of the serum C3 and C4 fraction of complement, cryoglobulin level, serum creatinine level, and a urinalysis to screen for hematuria and a 24-hour urine protein examination. The diagnosis of B-cell non-Hodgkin lymphoma (B-NHL) was made on the basis of evidence of BM, nodal, or extranodal lymphoproliferative disease with pathologic features that were compatible with the World Health Organization's classification of neoplastic diseases.[16] Treatment characteristics were also recorded.

Response to therapy

The clinical response of vasculitis was defined by analyzing the course of the following main clinical signs: skin involvement (absence of purpura or distal ulcers), peripheral neuropathy (clinical and/or electrophysiologic improvement at 2 successive examinations), renal involvement (normalization or improvement of glomerular filtration rate, proteinuria, and hematuria), and absence of arthralgia or arthritis. A complete clinical response was defined as an improvement in all baseline clinical manifestations. A partial response was defined as an improvement in at least one-half of the baseline clinical manifestations. All other patients were classified as nonresponders. A renal response was defined by a proteinuria < 0.5 g/d and/or the disappearance of hematuria and/or an improvement of the glomerular

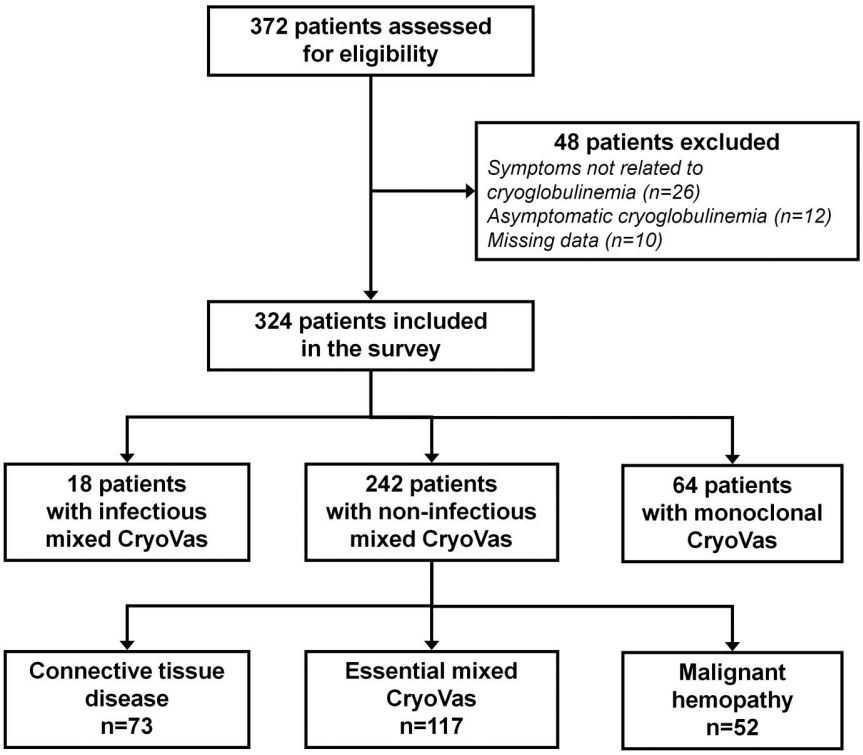

Figure 1. Flow chart of the CryoVas survey. Three hundred seventy-two patients were assessed for eligibility and 324 were finally included, including 242 patients with noninfectious MC vasculitis.

filtration rate (GFR) $>$ 20% in case of baseline GFR $<$ 60 mL/min/1.73m^2 (assessed with the Modified Diet in Renal Disease equation).[17] An immunologic response was defined as a $>$ 50% decrease in the baseline cryoglobulin level and/or a $>$ 50% increase in the serum C4 fraction. Relapse was defined as the reappearance of clinical signs of vasculitis.

Statistics

Descriptive statistics included the mean (SD) or median (minimum-maximum) as appropriate for continuous variables, and frequency (percentage) for categorical variables. Univariate analysis included the χ^2 or Fisher exact test as appropriate to compare categorical variables and the nonparametric Mann-Whitney test to compare continuous variables.

We first analyzed the efficacy and safety of different therapeutic regimen with the use of descriptive analysis. Efficacy (clinical, renal, and immunologic response) and safety (severe infection, death) were reported by treatment period. Each patient could thus be analyzed several times, according to the different treatments received.

We next evaluated the efficacy and safety of treatments after adjusting for confounding factors. Associations between prognostic factors and clinical response, serious infections, and death were tested with Cox time-dependent modeling. We also compared the efficacy and safety of different therapeutic regimen, that is corticosteroids alone versus combination therapy with corticosteroids plus immunosuppressive agents (alkylating agents or rituximab). To estimate the effect of treatment in the presence of time-dependent confounders[18-20] and in a situation in which treatment is varying through follow-up, we used Cox marginal structural models (Cox-MSMs). We created a pseudo population with the use of the inverse probability of treatment weighting, a method that calculates for each person, at any observed time, weights from the probability of persons receiving the treatment they actually received conditional on their observed covariates.[19-21] The baseline covariates included in the stabilized weights were age, sex, GFR, and cause of CryoVas. Because time-dependent variables were included in the model, vasculitis manifestations were gathered at each visit and before new treatment initiation. Several assumptions are, however, needed for the application of Cox-MSMs. Differences were considered significant when P values were $<$ .05.

Results

Patient characteristics

The characteristics of the 242 patients with noninfectious CryoVas are shown in Table 1. The mean age at diagnosis was 62.6 $\pm$ 14.5 years, and 163 patients (69%) were female. Clinical manifestations included cutaneous involvement in 201 patients (83%), peripheral neuropathy in 125 patients (52%), arthralgia/arthritis in 97 patients (40%), renal involvement in 84 patients (35%), gastrointestinal involvement in 13 patients (5%), and CNS and pulmonary involvement in 5 cases (2%) each. The mean cryoglobulin level was 0.94 $\pm$ 1.61 g/L, with 203 patients (84%) having type II MC.

The characteristics of patients with type II and type III-related CryoVas are shown in Table 1. Compared with patients with type III MC, patients with type II MC had more frequent purpura, peripheral neuropathy, and renal involvement; higher cryoglobulin levels; and lower C3 and C4 complement fractions and GFR.

The causative factors associated with noninfectious mixed CryoVas were connective tissue disease in 73 patients (primary Sjögren syndrome in 61 patients, systemic lupus erythematosus in 5, mixed connective tissue disease in 2, systemic sclerosis in 2, ulcerative colitis in 2, and rheumatoid arthritis in 1), hematologic disease in 52 patients (marginal zone lymphoma in 22 patients, low-grade B-NHL in 11, lymphoplasmacytic lymphoma in 10, follicular lymphoma in 2, mantle cell lymphoma in 2, chronic lymphocytic lymphoma in 2, and other B-NHL in 3), and essential mixed CryoVas in 117 patients (Figure 1).

No difference was found in the demographic and clinic-biologic presentation between patients with essential mixed CryoVas and B-NHL-related CryoVas, except for higher median cryoglobulin level in those with B-NHL (0.65 vs 0.30 g/L; P = .048). In

Table 2. Treatments received and efficacy and safety according to the cause of CryoVas, the therapeutic regimen used, and the line of treatment

	Causative factors				Efficacy, n/N (%)				Tolerance, n/N (%)	
	All patients	Essential MC	Connective tissue	Hematologic disease	Complete clinical response*	Renal response†	Immunologic response‡	Refractory disease§	Severe infection	Death
No.	209	92	71	46						
CTC alone										
First-line therapy, n	103	48	47	8	45/103 (44)	14/23 (61)	25/76 (33)	29/103 (29)	11/103 (11)	9/103 (9)
CTC, mg/d, median dosage (range)	50 (10-180)	55 (10-180)	40 (15-80)	55 (15-120)						
≥ Second-line therapy, n	45	23	17	5	15/45 (33)	10/17 (59)	17/38 (45)	12/45 (27)	5/45 (11)	6/45 (13)
CTC, mg/d, median dosage (range)	40 (10-80)	40 (10-80)	40 (15-60)	50 (20-80)						
Alkylating agents plus CTC										
First-line therapy, n‖	55	24	16	15	34/55 (62)	25/29 (86)	32/44 (73)	6/55 (11)	5/55 (9)	7/55 (13)
CTC, mg/d, median dosage (range)	60 (20-120)	60 (40-100)	50 (30-70)	50 (20-120)						
≥ Second-line therapy, n¶	28	17	9	2	11/28 (39)	8/12 (66)	11/23 (48)	6/28 (21)	2/28 (7))	1/28 (4)
CTC, mg/d, median dosage (range)	50 (7-70)	50 (10-70)	45 (7-60)	20 (20-20)						
Rituximab plus CTC										
First-line therapy, n#	28	14	4	10	18/28 (64)	11/13 (85)	17/22 (77)	3/28 (11)	8/28 (29)	3/28 (11)
CTC, mg/d, median dosage (range)	60 (20-80)	50 (20-80)	40 (20-60)	60 (50-70)						
≥ Second-line therapy, n**	58	23	29	6	38/58 (66)	15/17 (88)	41/49 (84)	3/58 (5)	11/58 (19)	5/58 (9)
CTC, mg/d, median dosage (range)	40 (5-80)	50 (10-80)	40 (5-80)	22.5 (15-40)						
Rituximab plus alkylating agents regimen										
First-line therapy, n††	12	1	0	11	10/12 (83)	7/7 (100)	8/10 (80)	0/12 (0)	5/12 (42)	3/12 (25)
≥ Second-line therapy, n‡‡	8	1	1	6	3/8 (38)	2/5 (40)	2/7 (29)	3/8 (38)	1/8 (13)	1/8 (13)
Alternative therapy										
First-line therapy, n	11	5	4	2						
≥ Second-line therapy, n	25	9	12	4						

CTC indicates corticosteroids.

*Complete clinical response was defined as an improvement in all baseline clinical manifestations.

†Renal response was defined by proteinuria < 0.5 g/d and/or the disappearance of hematuria and/or an improvement of GFR $> 20\%$ in case of baseline GFR < 70 mL/min/1.73m^2.

‡Immunologic response was defined as a $> 50\%$ decrease in the baseline cryoglobulin level and/or a $> 50\%$ increase in the serum C4 fraction.

§Refractory disease was defined as an improvement in less than one-half of the baseline clinical manifestations.

‖Including cyclophosphamide in 47 patients and chloraminophene in 8 patients.

¶Including cyclophosphamide in 25 patients and chloraminophene in 3 patients.

#Including the administration of 375 mg/m2/wk for 4 weeks in 23 patients and of 1000 mg at day +1 and day +15 in 5 patients.

**Including the administration of 375 mg/m^2/ per week for 4 weeks in 49 patients and of 1000 mg at day 1 and day 15 in 9 patients.

††Including rituximab/cyclophosphamide/prednisone in 9 patients and rituximab/cyclophosphamide/doxorubicin/vincristine/prednisone in 3 patients.

‡‡Including rituximab/cyclophosphamide/doxorubicin/vincristine/prednisone in 4 patients, rituximab/cyclophosphamide/prednisone in 3 patients, and rituximab/cyclophosphamide/fludarabine/prednisone in 1 patient.

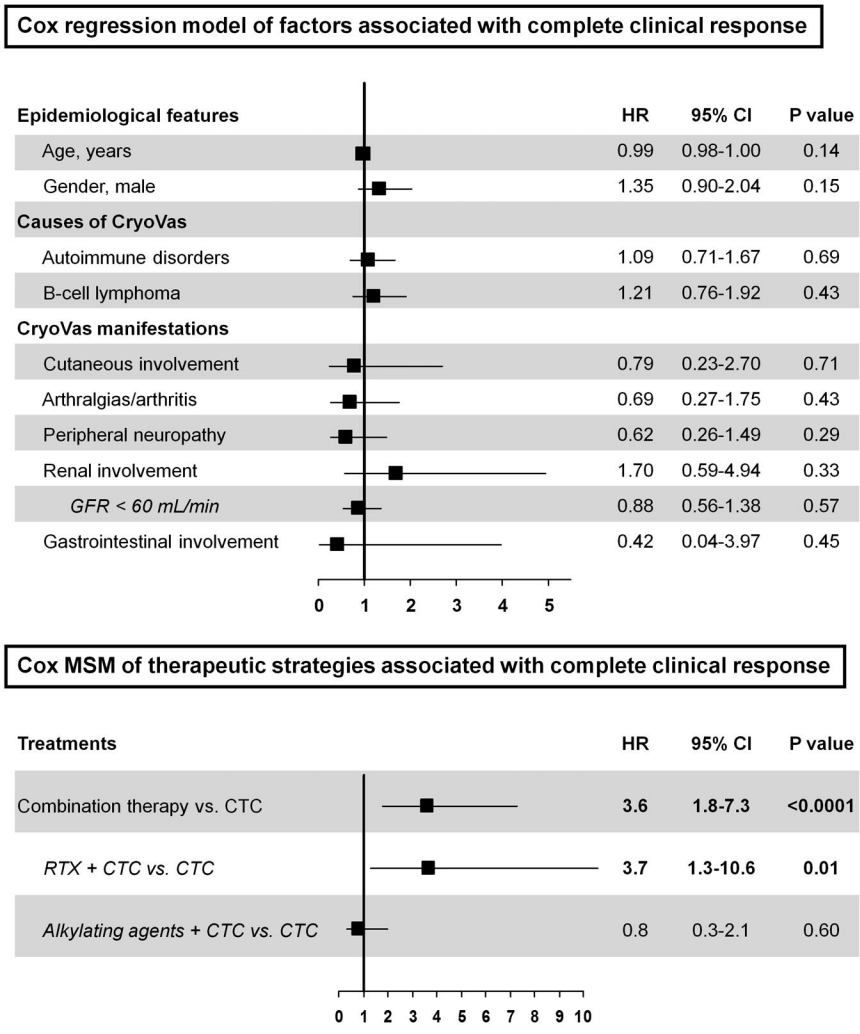

Figure 2. Cox time-dependent regression model and Cox-MSMs of factors and therapeutic regimen associated with a complete clinical response of noninfectious MC vasculitis. HR is indicated for each 10-year increase in age.

contrast, compared with patients with essential mixed CryoVas, patients with connective tissue disease were younger (59 ± 15 vs 63 ± 15 years; $P = .03$) and more frequently women (92% vs 58%; $P < .0001$), had more frequent peripheral neuropathy (63% vs 45%; $P = .02$), and tended to have less frequent renal involvement (25% vs 38%; $P = .08$).

Follow-up of patients

After a median follow-up of 54 months (interquartile range, 9-77 months) corresponding to 1028 patient-years, severe infections were noted in 55 patients (23%, 5.4 severe infections/100 patient-years), including bacterial septicemia in 19 patients, bacterial pneumonia in 11 patients, bacterial cutaneous infection in 11 patient, severe herpes virus infection in 4 patients, bacterial gastrointestinal infection in 2 patients, bacterial osteoarticular infection in 2 patients, pneumocystosis in 2 patients, endocarditis in 1 patient, and aspergillosis, cryptococcosis and candidiasis in 1 patient each. Nine patients developed B-NHL during follow-up, including 6 patients with primary Sjögren syndrome–related CryoVas and 3 patients with essential CryoVas.

Effect of therapeutic regimen on response to treatment and outcome

The data on 209 patients (86%) who received therapy (at least corticosteroids) and had an evaluable response to treatment were analyzed for outcome, that is, efficacy and tolerance of treatments, severe infections, and death. Treatments used in these patients during follow-up were corticosteroids in all patients, alkylating agents in 92 patients, rituximab in 85 patients, plasmapheresis in 43 patients, and azathioprine or mycophenolate mofetil in 31 patients. Patients received 1.8 ± 1.2 lines of treatments, totaling 373 treatment periods. The treatments and the median dosage of corticosteroids used for the patients according to the cause of CryoVas, and the treatment efficacy and safety for the different therapeutic regimen, that is, corticosteroids alone, alkylating agents plus corticosteroids, rituximab plus corticosteroids, and the combination of rituximab plus alkylating agents and corticosteroids, are reported in Table 2. Corticosteroids alone provided a complete clinical response and renal and immunologic responses in 44%, 61%, and 33% of patients in first-line therapy, respectively. Response rates to corticosteroids alone in refractory and/or relapsing patients were 33%, 59%, and 45%, respectively. First-line use of alkylating agents plus corticosteroids provided a complete clinical response and renal and immunologic responses in 62%, 86%, and 73% of patients, respectively. Response rates in refractory and/or relapsing patients were 39%, 66%, and 48%, respectively. First-line use of rituximab plus corticosteroids provided a complete clinical response and renal and immunologic responses in 64%, 85%, and 77% of patients, respectively. Response rates in refractory and/or relapsing patients were 66%, 88%, and 84%,

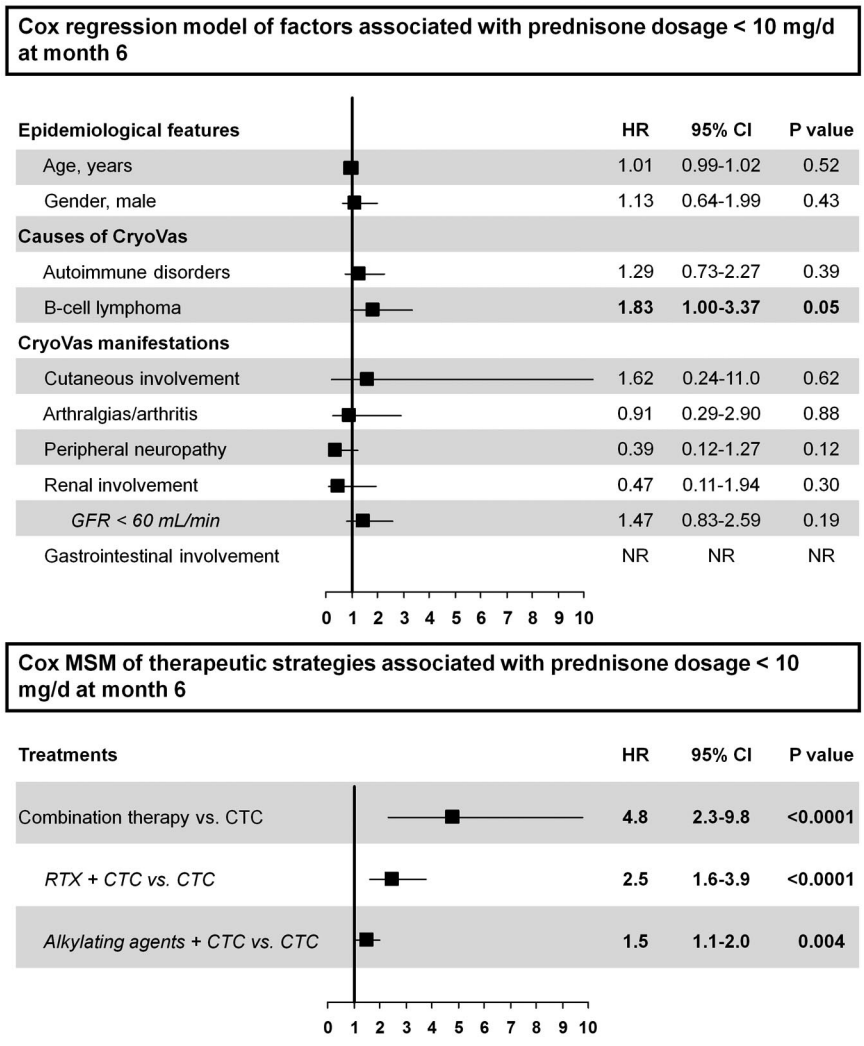

Figure 3. Cox time-dependent regression model and Cox-MSMs of factors and therapeutic regimen associated with a prednisone dosage < 10 mg/d at month 6 of the noninfectious MC vasculitis. HR is indicated for each 10-year increase in age.

respectively. Refractory response rates were higher with the use of corticosteroids alone, whereas rates of severe infections were higher with the use of rituximab plus corticosteroids. The efficacy of rituximab plus corticosteroids was similar when used in first- and second-line therapy. Alkylating agents plus corticosteroids and corticosteroids alone showed lower response rates when used as second-line therapy than as first-line therapy. The combination of rituximab plus alkylating agents and corticosteroids seems to provide a high efficacy, but the safety was poor with a high rate of severe infections (42%).

We next evaluated the efficacy and safety of treatments after adjusting for confounding factors. The results of the Cox regression model and Cox-MSMs of factors and therapeutic regimen associated with a complete clinical response and a prednisone dosage < 10 mg/d at month 6 (corticosteroid-sparing effect) are indicated in Figures 2 and 3. The association with renal and immunologic responses is indicated in supplemental Figures 1 and 2 (available on the *Blood* Web site; see the Supplemental Materials link at the top of the online article). The combination of rituximab plus corticosteroids was more effective than corticosteroids alone in achieving a complete clinical response (hazard ratio [HR], 3.7; $P = .01$; Figure 2), a decrease in prednisone dosage to < 10 mg/d at month 6 (HR, 2.5; $P < .0001$; Figure 3), a renal response (HR, 31.6; $P = .03$; supplemental Figure 1) and an immunologic response (HR, 33.8; $P = .001$; supplemental Figure 2). In contrast, a combination of alkylating agents plus corticosteroids was more effective than corticosteroids alone only in achieving a decrease in prednisone dosage to < 10 mg/d at month 6 (HR, 1.5; $P = .004$) and an immunologic response (HR, 5.7; $P = .001$). The results of the Cox regression model and Cox-MSMs of factors and therapeutic regimen associated with severe infections and death are indicated in Figures 4 and 5. Rituximab plus corticosteroids was associated with severe infections more frequently than corticosteroids alone (HR, 9.0; $P < .0001$), whereas the death rate did not differ between these 2 therapeutic regimen (HR, 1.7; $P = .40$). In patients who received rituximab, those with severe infection received high doses of corticosteroids more frequently than those without severe infection (dose > 50 mg/d in 71% of patients with infection vs 39% in those without infection, $P = .008$). In contrast, alkylating agents plus corticosteroids regimen was associated with severe infections less frequently than corticosteroids alone (HR, 0.2; $P = .002$), whereas the death rate did not differ between therapies (HR, 0.6; $P = .50$).

Discussion

Before the discovery of HCV in 1989, MC vasculitis was considered an essential or idiopathic disease in most cases. The systematic HCV screening performed in these patients found that most of the

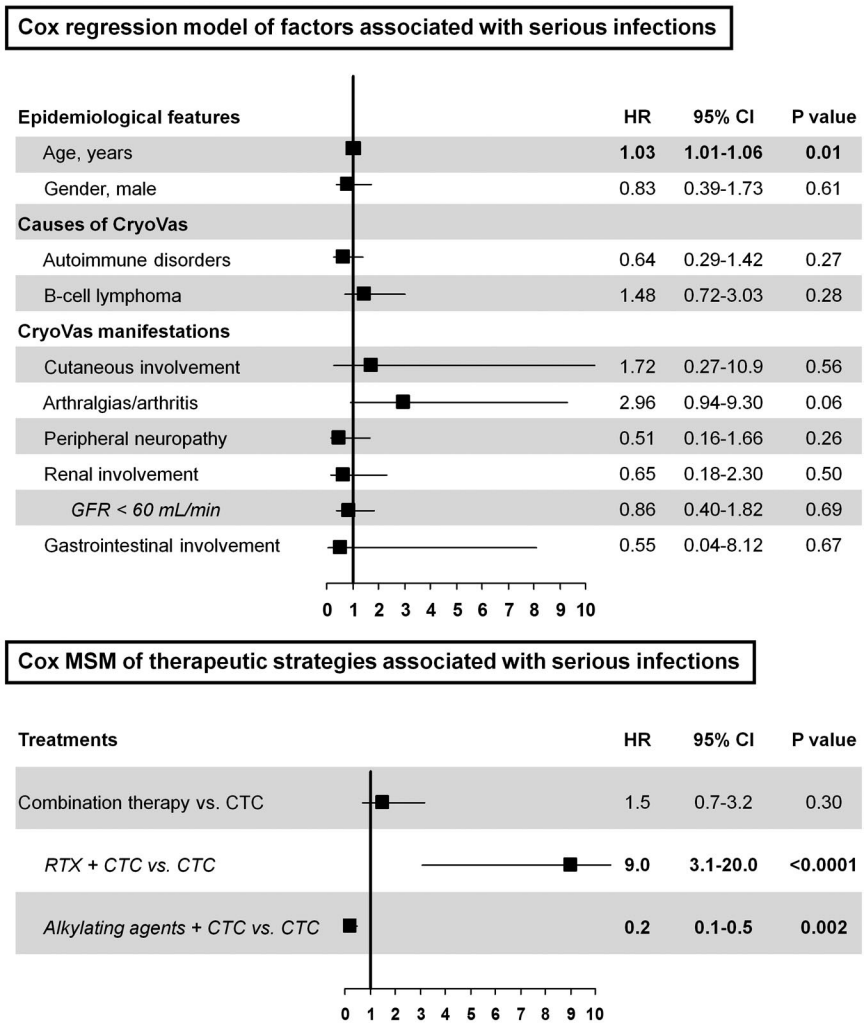

Figure 4. Cox time-dependent regression model and Cox-MSMs of factors and therapeutic regimen associated with serious infections in noninfectious MC vasculitis. HR is indicated for each 10-year increase in age.

patients with mixed CryoVas are positive for HCV infection markers.[2-5] Along this line, most of the previous data on the presentation, prognosis, and therapeutic management of mixed CryoVas, derived from old studies that included HCV-positive and -negative patients, should thus be interpreted with caution and revisited according to HCV status. In the past decade, it has been clearly reported that the therapeutic management and prognosis of HCV-related vasculitis differed from that of HCV-negative patients.[4,22-24] To better define the clinical spectrum and the therapeutic management of noninfectious mixed CryoVas, we analyzed the data from 242 patients included in the French multicenter and transdisciplinary CryoVas survey, which constitutes the largest series reported so far in the literature.

This study describes the spectrum of clinical presentation and causative factors of noninfectious mixed CryoVas. For demographics, both the mean age at the time of diagnosis and the sex ratio (predominance of females) were in keeping with what had been previously reported in large series of HCV-positive patients[24] and small series of HCV-negative patients.[4,5] Rates for cutaneous, articular, and renal involvement in the present study were comparable with those found in HCV-positive patients, whereas peripheral neuropathy seemed to be more frequent in the latter than in noninfectious mixed CryoVas (74% vs 52%).[24] Our survey confirms that connective tissue diseases and, in particular. primary Sjögren syndrome, hematologic disorders, and essential mixed CryoVas remain the main causes of noninfectious mixed CryoVas, with a slightly higher rate of essential mixed CryoVas.[4] These findings reinforced the idea that patients with mixed CryoVas should be systematically screened for the presence of these disorders which could modify the prognosis and the therapeutic management.

We decided to include only patients with mixed CryoVas and to exclude those with type I monoclonal CryoVas, because these patients differ in their causes, clinico-biologic presentation, outcome, and therapeutic management. In contrast to mixed CryoVas, type I monoclonal CryoVas is always related to B-cell lymphoproliferative disorders, mainly lymphoplasmacytic and plasmacytic lymphoproliferative disorders. Type I monoclonal CryoVas differs from mixed CryoVas by more frequent severe cutaneous involvement and higher serum cryoglobulin levels. These differences in their presentation are related in part to the absence of rheumatoid factor activity of type I cryoglobulins and their decreased ability to activate the complement pathway. Along this line, cutaneous manifestations are frequently the consequence of a hyperviscosity-related vasculopathy rather than an immune complex-induced vasculitis.

Because randomized controlled trials are lacking in the literature, the evaluation of efficacy and safety of the different therapeutic regimens was a main goal of the CryoVas survey to improve the management of noninfectious mixed CryoVas patients. The descriptive analysis provided interesting findings on the efficacy and the safety of the different therapeutic regimen. The efficacy of

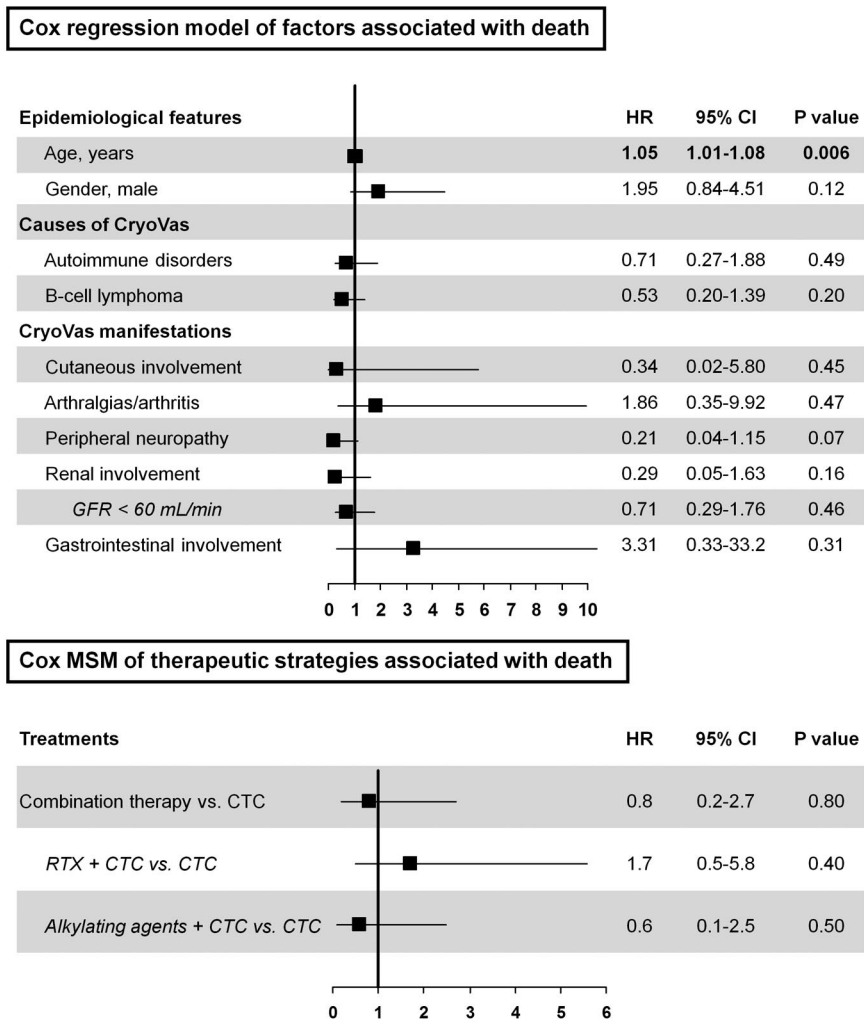

Figure 5. Cox time-dependent regression model and Cox-MSMs of factors and therapeutic regimen associated with death in noninfectious MC vasculitis. HR is indicated for each 10-year increase in age.

alkylating agents plus corticosteroids and of rituximab plus corticosteroids was similar when used in first-line therapy, whereas rituximab plus corticosteroids seemed to provide a better efficacy in relapsing and/or refractory patients. However, rates of severe infections were higher with the use of rituximab plus corticosteroids. We next decided to analyze the effect of treatments after adjustment for the time-dependent confounders with the use of Cox-MSMs, which had been previously used in observational studies.[18-20] Although Cox-MSMs cannot include all time-dependent confounders, covariates included in the model (ie, age, sex, GFR, cause of CryoVas, vasculitis manifestations, and the presence of a relapsing or refractory disease) represent the main time-dependent confounders. With the use of Cox-MSMs, rituximab plus corticosteroids combination therapy showed the greater efficacy compared with corticosteroids alone and alkylating agents plus corticosteroids for clinical, renal, and immunologic responses and corticosteroid-sparing effect. In contrast, the rituximab plus corticosteroids regimen was associated with more frequent severe infections, particularly when high doses of corticosteroids were used. This increased risk of severe infections was not observed with alkylating agents plus corticosteroids regimen, but this regimen seemed to provide lower response rates than rituximab plus corticosteroids. The efficacy of rituximab in noninfectious CryoVas was recently reported in a small series of 23 patients,[10] with rituximab showing a clinical and immunologic response in $> 80\%$. Besides this dramatic efficacy, the occurrence of severe infections with similar rates compared with our survey was described. These infections occurred in a particular subset of patients, characterized by older age, renal failure (GFR < 60 mL/min), and the use of high-dose corticosteroids. Overall, these findings suggest that rituximab plus corticosteroids could be the first therapeutic option in patients with severe noninfectious mixed cryoglobulinemia vasculitis but that corticosteroids should be rapidly tapered to decrease the risk of severe infection. The role of rituximab as first-line treatment in nonsevere patients remains to be determined.

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Authorship

Contribution: B.T., O.H., J.-M.L., X.M., P.S., E.P., and P.C. designed the research; B.T., I.M., D.L., A.L., P.B., L.d.S.-M., T.Q., A.H., F.B., G.L.G., J.-E.K., O.H., P.R., E.D., E.L., F.B., T.Z., O.H., J.-M.L., X.M., P.S., E.P., and P.C. collected data; B.T., E.K., F.C., and P.C. analyzed and interpreted data; E.K. and F.C. performed statistical analysis; and B.T. and P.C. wrote the manuscript.

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