Autoimmune hemolytic anemia in chronic lymphocytic leukemia: clinical, therapeutic, and prognostic features
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Fifty-two cases of autoimmune hemolytic anemia (AHA) were observed within a series of 1203 patients (4.3%) with chronic lymphocytic leukemia (CLL) followed at a single institution. Nineteen were observed at the time of CLL diagnosis and 33 during the clinical follow-up. Ninety percent of the patients with CLL/AHA showed active CLL and 25% had been treated previously. The antienzyme autoantibody (AeAb) was an IgG in 87% of cases and an IgM in 13%. A lymphocyte count more than 60 x 10^9/L (P < .00001), age above 65 years (P < .01), and male gender (P < .01) emerged as independent parameters that correlated significantly with an increased rate of AHA at CLL diagnosis. Patients previously treated with chlorambucil (CB) plus prednisone (PDN) and with fludarabine plus PDN showed a similar rate of AHA (1.8% and 2.5%, respectively). After steroid therapy associated with CB in case of active CLL, 70% of patients achieved the complete disappearance of the AeAb. The actuarial AHA relapse-free survival probability was 54% at 5 years and the median survival probability after AHA was 41 months. Infections represented the main cause of morbidity and mortality. IgG AHA and the occurrence of AHA at the same time of CLL diagnosis emerged as independent factors significantly correlated with a better survival probability of AHA/CLL patients. Taken together, this study indicates that in CLL, AHA is a rare event with no independent effect on survival for which steroids, associated with CB if required, and a careful management of infections may successfully control the 2 conditions. Cooperative studies are needed to better define the optimal steroid schedule and the therapeutic role of other immunosuppressive agents and splenectomy. (Blood. 2000;95:2786-2792)

Introduction

Autoimmune phenomena are a well-known complication of lymphoproliferative diseases, in particular of chronic lymphocytic leukemia (CLL).1-3 Three autoimmune hematologic conditions frequently associated with CLL are autoimmune hemolytic anemia (AHA), idiopathic thrombocytopenic purpura, and pure red cell aplasia.4 Of these, AHA is the most frequent autoimmune disorder described in CLL and, conversely, CLL is the hematologic malignancy in which AHA occurs most frequently.5 It has been estimated that between 3% and 37% of patients with CLL develop AHA.6-8 Previous studies have shown that AHA is usually observed in advanced stages of the disease and that CLL patients with AHA represent a poor prognosis category.2,6-8 Moreover, the National Cancer Institute (NCI)-Sponsored Working Group Guidelines for CLL9 included AHA among CLL-related signs of active disease. Therapeutic approaches, such as radiation and alkylating agents,10,11 particularly cyclosporine27, have been considered as risk factors for the occurrence of AHA. It is thought that the imbalance among lymphocyte subsets, contributed by therapy, could result in the emergence of an autoimmune clone. However, the exact mechanisms leading to autoimmunity in CLL are still unclear and have been the subject of several biologic studies.20-25

Although the association of AHA with CLL is well known, the literature is based mainly on small series of patients or on isolated case reports. Thus, there is limited information on the clinical features and outcome of these patients. Up to now, no established standard therapy for CLL/AHA patients has been recognized. Patients are usually treated with prednisone (PDN) according to the schedule proposed by Dameshek et al26 in 1956, although other treatment modalities have been used in unresponsive AHA patients (eg, cytotoxic drugs, intravenous immunoglobulins, and cyclosporine27).

To better define the features of AHA associated with CLL, we have retrospectively analyzed, in a large series of 1203 CLL cases followed at a single center over 10 years, the clinical, serologic, prognostic and therapeutic characteristics of 52 patients who developed AHA. The main objectives of the study were to evaluate the effect of AHA on survival of CLL patients, the risk factors for developing AHA, and the prognostic factors influencing survival of AHA/CLL patients.

Patients and methods

Case series and diagnosis of AHA

Between 1986 and 1996, 1203 CLL patients have been diagnosed and managed at the Institute of Hematology of the University “La Sapienza” of Rome. The cut-off date of analysis was May 1999. In 52 cases (4.3%), clinical and laboratory features of AHA were recorded. For the diagnosis of CLL, the cytomorphologic and immunologic criteria recommended by the NCI9 were applied. All patients were subsequently seen every 1 to 3 months
according to the course of the disease and on each occasion a full blood count was obtained.

In all CLL patients with evidence at any time during the course of the disease of anemia (hemoglobin < 12 g/dL) or one or more laboratory signs of hemolysis (increased bilirubin, increased lactate dehydrogenase, reticulocytosis), an immunohematologic workup was performed. Patients showing anemia, associated with the presence of antienzyme autoantibody (AeAb), were considered as CLL with AHA (CLL/AHA). The presence of AeAb was analyzed on the red blood cells and in the serum of patients. Briefly, the AeAb and the complement bound to the red cell membrane were detected by the direct antiglobulin test (DAT) using a broad-spectrum antisera (Ortho Diagnostic Systems, Raritan, NJ). The immunoglobulin class of the AeAb and the presence of the C3d were defined with monospecific antisera (anti-IgG, anti-IgA, anti-IgM, anti-C3d) (CLB, Amsterdam, The Netherlands). Eluates were performed to determine the specificity of the AeAb. In the presence of IgM autoantibodies, the thermal amplitude range and titer were defined.

Therapy

Patients with evidence of AHA were managed as follows: all patients were treated with PDN (1-2 mg/kg body weight daily). In addition to PDN, previously untreated patients with other clinical signs of active CLL as defined by the NCI criteria (high and progressive lymphocyte count, massive increase of nodal and/or spleen size, and so forth) received chlorambucil (CB; 10 mg/m²/d for 6 consecutive days monthly). Seven patients developed AHA while on low doses of CB, as “maintenance therapy,” and were treated with CB and steroids at the above doses. Three patients developed AHA after the first, fifth, and sixth course of fludarabine (FD) plus PDN. FD was discontinued, 2 patients with complete response (CR) received PDN alone, and the last patient with progressive disease was treated with PDN plus CB given at the above doses. In patients responsive to therapy (see below the criteria for the definition of complete or partial AHA response), the initial dose of steroids was slowly tapered by 5 mg every 1 or 2 weeks. After 6 months of therapy, patients with persistent response of AHA and CLL were “maintained” on low-dose PDN (5-10 mg 3 times a week) and CB (5 mg 3 times a week), if the latter had been administered.

Definition of response of AHA and CLL

The AHA response was assessed according to the weekly evaluation of the hemoglobin values combined with the monthly evaluation of the Coombs test. The following criteria were applied to define the response of AHA: (1) patients with no detectable AeAb and persistent hemoglobin values of 12 g/dL or higher were considered as complete responders (CR); (2) patients with persistent AeAb but with a hemoglobin increase to 12 g/dL or higher or of at least 3 g/dL were considered as partial responders (PR); (3) patients with persistent AeAb in the absence of a significant hemoglobin increase (< 3 g/dL) were considered as “failures.”

In patients with a persisting response of AHA (CR/PR), the immunohematologic follow-up evaluation was performed every 3 to 6 months.

The response of CLL to therapy was defined according to the criteria proposed by the NCI. 9

Supportive care

Considering the risk of opportunistic infections due to the underlying disease and to therapy itself, the last 29 patients received trimethoprim-sulfamethoxazole as prophylaxis against Pneumocystis carinii infection from the start of steroid therapy. Irradiated packed red cells were infused in the presence of severe and symptomatic anemia.

Statistical methods

Three different points were analyzed by multivariate analysis. The first analysis was focused on factors related to the occurrence of DAT-positive or DAT-negative anemia at the same time as the CLL diagnosis. The 1203 CLL patients of this series were analyzed and cases of DAT-positive or DAT-negative anemia recorded at the time of CLL diagnosis were considered as events. The following parameters observed at the time of CLL diagnosis were analyzed: gender (male versus female), age (≥ 65 years versus > 65 years), lymphocyte count (≥ 60 versus > 60 x 10³/L). The hemoglobin level and stage were excluded to avoid an overlap effect; anemia is in fact defined by hemoglobin and the levels of hemoglobin define the stage of the disease.

The second analysis was carried out on the entire series of 1203 CLL cases to define the prognostic relevance of AHA and other variables at the time of the diagnosis of CLL. For this purpose, the following parameters were analyzed: gender (male versus female), age (≥ 65 years versus > 65 years), lymphocyte count (≥ 60 versus > 60 x 10³/L), platelets count (≥ 100 versus > 100 x 10³/L), DAT-positive anemia (yes versus no), DAT-negative anemia (yes versus no).

The third analysis was performed to identify the prognostic importance of different factors within the group of 52 CLL patients with AHA. The following parameters observed at the time of AHA diagnosis were analyzed: gender (male versus female), age (≥ 65 years versus > 65 years), lymphocyte count (≥ 60 versus > 60 x 10³/L), platelets count (≥ 100 versus > 100 x 10³/L), time of AHA diagnosis (at CLL diagnosis versus after CLL diagnosis), the Ig class of the AeAb (IgG versus IgM), previous therapy for CLL (yes versus no), the hemoglobin value at AHA diagnosis (< 8 versus ≥ 8 g/dL), and the administration of infection prophylaxis (yes versus no).

The rate of AHA was evaluated according to the type of previous therapy (CB plus PDN in 559 patients versus FD plus PDN in 121 patients). The actuarial probability of achieving a CR of AHA and the AHA relapse-free survival probability were analyzed. The corrected χ² test was applied to compare groups. To evaluate the relative importance of clinical variables, a multivariate logistic regression model was used from which adjusted odds ratio and 95% confidence intervals (CIs) were derived. Survival curves were calculated according to Kaplan and Meier, and compared with the log-rank test. The relative significance of different factors on survival was evaluated by the multiple regression model from which hazard ratios and 95% CIs were derived. Analyses were performed with the package BMDP Statistical Software (Los Angeles, CA).

Results

Clinical characteristics of CLL patients with AHA

A diagnosis of AHA was made in 52 of the 1203 patients (4.3%) observed at our institution. The median age was 69 years (range, 49-89 years); 44 were men. The median hemoglobin value at the time of AHA diagnosis was 8 g/dL (range, 4.9-9 g/dL). The AeAb was of the IgG class in 45 patients (87%) and of the IgM class in 7 patients (13%). In all 45 patients with IgG AHA, the presence of the autoantibodies on the red cell membrane was detected by DAT, which revealed also the presence of C3d in 38 of these cases. In 41 of 45 (91%) patients positive for IgG, the autoantibody was present also in their serum.

Of the 7 patients in whom an IgM AeAb was detected in the serum, 4 showed also a positive DAT for C3d. In all cases, the IgM autoantibodies were reactive at 37°C, with titers at 4°C ranging between 1:256 and 1:8192. The autoantibody specificity was directed to the “ε” antigen in 5 evaluable cases of IgG AHA and to the “ε” antigen in the 7 cases of IgM AHA.

One or more indirect signs of hemolysis were present in all cases. The large majority of patients (47; 90%) showed clinical features of active CLL. In 19 patients (37%), AHA was observed at the same time as the diagnosis of CLL and in 33 (63%) during the course of the disease, after a median time of 36 months (range, 9-136) from the diagnosis of CLL. Among the 33 patients with late AHA, 13 had been previously treated and 20 were untreated. This means that altogether, 39 patients (75%) were untreated at the time of the diagnosis of AHA. Of the 13 patients previously treated, 10 developed AHA while on therapy, 7 on low doses of CB, and 3 after...
FD plus PDN (first-line therapy: 1 patient; second-line therapy: 2 patients); the remaining 3 patients were off therapy from CB plus PDN after 15, 18, and 60 months, respectively. Of the 3 patients on FD plus PDN, 2 were in CR after, respectively, the fifth and the sixth course of therapy, and 1 patient showed an unresponsive disease after the first course. None of the patients who developed AHA after FD were re-treated with FD.

Clinical parameters related to the occurrence of AHA and prognostic significance of AHA

According to the multivariate analysis carried out on the entire series of 1203 patients, lymphocyte count ($P < .00001$), age ($P = .01$), and gender ($P < .01$) emerged as independent factors significantly related to the occurrence of DAT-positive anemia (AHA) at the time of CLL diagnosis. A higher lymphocyte count, older age, and male gender were significantly linked with an increased rate of AHA at CLL diagnosis (Table 1). It is worth noting that the lymphocyte count was associated with a high 95% CI(8.23-62.6). When the occurrence of DAT-negative anemia at CLL diagnosis was analyzed, 2 independent parameters emerged as significant factors: lymphocyte count ($P < .00001$) and age ($P = .04$), whereas gender was not significant (Table 1).

At the time of the diagnosis of AHA, only 13 of 52 patients (25%) had been treated previously. The rate of AHA cases observed among patients treated with CB plus PDN (10 of 559, 1.8%) and with FD plus PDN (3 of 121, 2.5%) was not statistically different ($P = .8$).

The multivariate analysis performed on the entire series of 1203 patients to define the relative prognostic significance of AHA and of other parameters recorded at the diagnosis of CLL revealed 4 independent factors significantly correlated with survival probability at 10 years: lymphocyte count ($P < .0001$), gender ($P < .0001$), age ($P = .01$), and anemia ($P < .0001$). However, when the effects of DAT-positive anemia (AHA) and DAT-negative anemia were evaluated separately, only DAT-negative anemia was an independent factor significantly related to survival ($P < .00001$) (Table 2).

Response to therapy of AHA

Fifty of the 52 patients with AHA/CLL were assessed for response to therapy; 2 were lost to follow-up. Therapy consisted of PDN alone in 4 patients with stable CLL and of PDN associated with CB in the remaining 46 with active CLL. Forty-two patients (84%) achieved a response (CR plus PR). The median time to reach hemoglobin values of 12 g/dL or higher was 4.5 months. Thirty-five patients (70%) obtained a CR with the disappearance of the AeAb. The actuarial median time probability to obtain the CR was 6 months. The last CR was achieved after 24 months from the start of therapy.

At the time of this report, 7 of 50 patients (14%) are in PR; they promptly reversed to a normal hemoglobin value without the disappearance of the AeAb that is still present after a median time of 12 months (range, 6-24 months) from the start of therapy. Eight patients (16%) were considered as “failures” because they showed no improvement in hemoglobin values. The median age of the unresponsive patients was 74 years. In 4 cases, 3 previously treated with CB plus PDN, an inadequate reticulocytosis was recorded and the corresponding marrow was hypocellular with dysplastic erythropoiesis. In the other 4 patients, the hematologic picture was dominated by the presence of active CLL. Recurring infections represented the main impediment to use of an alternative therapy. Furthermore, none of the 8 unresponsive patients showed a clinical picture adequate to face a splenectomy. In only 3 patients, a second-line therapy consisting of high doses of intravenous immunoglobulins (IVIG) and PDN in 1, IVIG plus PDN and azathioprine in another, and of IVIG plus PDN plus cyclosporine in the last was attempted. Unfortunately, the 3 patients died without evidence of an improvement of the hemoglobin values. Taken together, the 8 patients considered as “failures” died after a median time of 2 months (range, 1-6 months) mainly due to infection (6 of 8 patients). The response rate (CR plus PR) of the 12 evaluable patients who developed AHA after previous treatment was lower, though not significantly, compared to that in the 38 previously untreated patients (67% versus 89%; $P = .1$).

AHA and CLL activity

In 47 of 52 patients (90%), the onset of AHA was associated with active CLL. Of the 46 evaluable patients with active disease, 87% achieved a response of both CLL and AHA, 4% obtained only a response of CLL, and 9% failed to show any improvement.

The response of AHA was obtained after steroids in 2 of 4 evaluable patients with stable CLL.

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<th>Factors at CLL diagnosis</th>
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*Patients with DAT-positive anemia (AHA) at CLL diagnosis excluded (19 patients).
†Patients with DAT-negative anemia at CLL diagnosis excluded (97 patients).
Relapses of AHA

Eight of the 35 patients (23%) who obtained a CR of AHA relapsed after a median time of 19 months from the achievement of the response (range, 6-45 months). The actuarial relapse-free survival probability from CR was 54% at 5 years. All patients relapsed while on maintenance therapy with low-dose CB plus PDN (6 patients) or PDN alone (2 patients). In 5 relapsed patients, the Ig class of the AeAb was of the same Ig class observed at the time of the first hemolytic episode (IgG, 4; IgM, 1). The remaining 3 patients, in whom the first episode was due to an IgG, showed at recurrence an IgM in the first case, an IgG plus IgM in the second case, and an IgG plus IgM plus IgA in the last. Therapy for AHA relapses consisted of PDN in 3 patients and of CB plus PDN in 5. A new response of AHA was achieved by all 7 evaluable patients (3 CR).

Toxicity and survival of CLL patients with AHA

The occurrence of infections represented the main cause of morbidity and mortality. Twenty-seven patients (52%) showed an infection that was a pneumonia in the majority of cases (21 cases). Three cases of septicemia and 6 viral infections (herpes varicella-zoster, 4 cases; cytomegalovirus interstitial pneumonia, 1 case; hepatitis B, 1 case) were also observed. Nine patients experienced steroid-related hyperglycemia requiring oral hypoglycemic agents or insulin and in 1 patient a peptic ulcer was diagnosed.

Twenty-eight of the 52 patients (54%) have died. Infections represented the main cause of early mortality within 12 months from the diagnosis of AHA (7 of 12 patients, 58%) and of the overall mortality (15 of 28 patients, 54%). Deaths directly related to CLL accounted for 28% of cases (8 patients) and 1 patient died with progressive CLL associated with intestine cancer (3.5%). After 34 months from the diagnosis of AHA, a partially responsive patient developed a pure red cell aplasia and died. In 3 patients, the cause of death could not be evaluated.

The overall median actuarial survival probability from the diagnosis of AHA was 41 months.

At multivariate analysis, 2 independent factors appeared significantly related to survival probability of CLL patients with AHA: the Ig class of the AeAb ($P = .02$) and the time of AHA occurrence ($P = .02$). Patients with IgM autoantibody and those with late occurrence of AHA had a significantly lower chance of survival (Table 3 and Figure 1).

Transfusion therapy

Selected and irradiated red cells were given to 6 patients with severe (median hemoglobin value, 5.3 g/dL) and symptomatic anemia. None of the 6 transfused patients developed any clinical or laboratory evidence of transfusion reactions.

Discussion

We have described in a series of 1203 incidental CLL cases followed at a single institution the clinical and prognostic
Additionally, an impaired function of the aged thymus may lead to an imbalance among autoregulatory CD4+ and autoreactive T-lymphocyte subsets that may predispose to autoimmunity.34

In our series, the large majority of patients showed clinical signs of active CLL at the time of AHA diagnosis and, after therapy, achieved a response of both CLL and AHA. This clinical finding indicates a very close relationship between the activity of CLL and AHA. This may be explained by the biologic correlation between CLL and autoreactivity, because CD5+ B cells are involved in both. In some cases, direct evidence that the AeAbs were produced by leukemic CLL clones could be demonstrated.35 Furthermore, Efremov et al34 recently reported that in approximately half of AHA/CLL patients there is a preferential expression of 2 Ig VH gene segments, 51p1 and DP-50, in association with a particular CDR3 region by the leukemic cells, suggesting the possibility that CLL cells may be directly involved in the pathogenesis of AHA. However, in the majority of cases of AHA the autoantibodies are of the IgG class. It is unlikely that such autoantibodies may represent the direct product of the CD5+ B-cell clone, because IgG autoantibodies are in fact almost always polyclonal, whereas cultures of leukemic cells usually produce monoclonal IgM with low affinity and cross-reactive idiotypic activity.22 This point is supported by the observation that mice with severe combined immunodeficiency engrafted with peripheral blood lymphocytes from CLL patients frequently develop polyclonal IgG AeAb.36

To explain the emergence of autoimmunity, it has also been argued that a deep immunodeficiency, frequently related to active and advanced stage CLL,37 may favor the emergence of a CD5- B-lymphocyte clone producing AeAb. However, the probability that CLL patients with AHA may be more profoundly immunocompromised needs to be specifically addressed. An alternative pathogenetic mechanism that can be postulated to explain the relationship between AHA and active CLL may be a defective lymphocyte apoptotic program. Recently, a novel disorder termed autoimmune lymphoproliferative syndrome characterized mainly by the proliferation of TCR double-negative T cells, the enlargement of lymph nodes and spleen, and the presence in some cases of AHA or other autoimmune manifestations has been described.38-40 The affected patients show a heterozygous Fas gene mutation with a deficient Fas molecule that leads to a defective lymphocyte apoptosis. The Fas mutation seems to represent a susceptibility factor for autoimmune diseases, as for deficiencies of other molecules involved in lymphocyte homeostasis.40 The Fas/Fas ligand system that regulates B-cell interactions plays a role in the elimination of autoreactive B lymphocytes.41 A similar defective Fas system characterized by a negative or faint cell surface Fas receptor expression42 and the resistance to the Fas-mediated cytotoxic pathway43 has been described in CLL; this may predispose to the accumulation of leukemia cells and also to the emergence of autoimmune disorders.

After therapy, 70% of patients achieved the disappearance of the AeAb. However, this does not always correspond to the complete eradication of a specific B-lymphocyte clone producing the AeAb; 23% of responder patients, in fact, relapsed. It is of biologic interest that in 3 cases a different Ig class of autoantibody was detected at the time of AHA relapse. This finding could suggest in CLL patients developing AHA the presence of an immune dysregulation background, rather than a relapsing single autoimmune B-cell clone.

A hypothetical pathogenetic role of therapy may be postulated for a small proportion of cases, because only 25% of patients had been previously treated at the time of AHA onset. In our series, FD plus PDN did not emerge as a treatment with an increased risk of
inducing AHA compared to CB plus PDN. The early or delayed development of AHA after FD therapy in CLL patients has been widely described. It is generally thought that FD may predispose to AHA by inducing a marked lymphocytopenia, particularly of CD4+ lymphocytes, with a T-cell subset imbalance that may favor the emergence of autoreactive T cells. In CLL patients treated with FD alone, the incidence of AHA reported by Byrd et al, Di Raimondo et al, and Mynt et al ranged between 11% and 21%. The lower incidence of AHA observed in our series after FD plus PDN therapy is probably related to 3 different factors. First, none of our treated patients had a previous history of AHA prior to FD treatment. Second, our patients were relatively “young” (median age, 53 years) compared to those described by Di Raimondo et al (median age, 60 years). Mynt et al (median age, 59 years), and Weiss et al (median age, 68 years). The younger age could represent a lower factor of risk for the development of AHA. Third, our patients were not all heavily pretreated because in half of them FD was given as first-line treatment. A similar low rate of AHA observed among patients treated with FD as first-line therapy has been recently reported by a French study. It would be useful to analyze in a larger series of patients treated with FD the relative risk of developing AHA related to the above mentioned factors: previous history of AHA and or DAT positivity, previous treatment, age, and addition of PDN to therapy. The knowledge of such risk factors could be of help in guiding the treatment choice for CLL patients.

The high overall response rate obtained after therapy, particularly in the preponderant IgG-AHA patients, indicates that steroids, alone or associated with CB in the presence of active CLL, were very effective as front-line therapy. However, the morbidity and early mortality due to infections represented an important cause of failure in AHA/CLL patients. Infections, observed in the majority of unresponsive patients, may in fact inhibit an optimal hematopoietic activity and points to an immunodeficiency state further worsened by therapy. Steroids have been related to an increased incidence of atypical infections in CLL patients treated with FD. According to Anaissie et al, CLL patients with AHA because of advanced stage and corticosteroid therapy identify a subset at risk of serious infections in which prophylaxis should be considered. However, in our series, the prophylactic administration of trimethoprim-cotrimoxazole did not influence survival of AHA/CLL patients. The reduction of dose and duration of steroid therapy, possibly the administration of IVIG, and careful monitoring and management of infections should be evaluated in an attempt to overcome the operating vicious circle: immunosuppression, infections, and treatment failures.

In our patients, splenectomy was not considered as first-line treatment and none of the 8 unresponsive patients showed a clinical picture adequate to face a surgical approach. Considering its steroid-sparing property, the possible benefit of splenectomy should be evaluated in the earlier therapeutic management of unresponsive patients.

According to multivariate analysis, 2 independent factors were significantly related to better survival probability of CLL patients with AHA: the IgG class of the AeAb and the occurrence of AHA at the time of CLL diagnosis. Patients with IgM AeAb identified a small group with very poor survival. In these cases, the IgM AeAb was a “warm” complete antibody, optimally reactive at 37°C. IgM AHA with such serologic findings is usually uncommon and has been described in idiopathic cases of mixed IgG/IgM AHA also characterized by poor clinical outcome. In conclusion, this study indicates that AHA is a rare event in CLL with a significantly higher incidence in older patients, male patients, and in patients with active CLL; it has no independent effect on survival probability. Steroids associated with CB therapy, if required, and careful management of infections may be considered a potentially successful therapeutic approach for the management of patients with AHA/CLL. However, cooperative studies are needed to better define the optimal steroid schedule and the therapeutic role of other immunosuppressive agents and splenectomy for the treatment of patients with AHA/CLL.

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