show that low-dose alemtuzumab in pretreated CLL patients can induce a good ORR and is associated with only mild hematologic and extrahematologic side effects and a low rate of infectious diseases, even though severe immunosuppression can persist for prolonged periods. The reduction in infections could be exploited by combining low-dose alemtuzumab therapy with chemotherapy in order to increase responses to treatment.

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Chronic Lymphocytic Leukemia

Multiple lines of chemotherapy are the main risk factor for severe infections in patients with chronic lymphocytic leukemia with febrile episodes

We report on febrile episodes occurring among 379 patients affected by chronic lymphocytic leukemia, observed from 1984 to 2002. One hundred and twenty eight patients (33.7%) developed 341 febrile episodes, of which 251 were documented infections (82 severe and 169 moderate). Among various risk factors, only previous treatment with multiple regimens of chemotherapy was associated with severity of infection (p=0.0005).

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Infections are the major cause of morbidity and mortality in patients with chronic lymphocytic leukemia (B-CLL).[1,2] Some conditions known to be risk factors for the development of infections are age, decreased levels of immunoglobulins,[3,4] Binet stage,[5] neutropenia,[6] treatment with fludarabine,[7,8] treatment with more than one line of chemotherapy.[9]

We analyzed the medical records of all patients affected by B-CLL referred to our hospital between 1984 and 2002 and evaluated all the febrile episodes observed during the follow-up of these patients. All events, even if occurring at home and treated by a general practitioner or leading to admission to other hospitals, are usually precisely recorded in our own hospital records. In this long period patients were heterogeneously treated: at the beginning of data collection, first-line therapy was chlorambucil and salvage therapy was polychemotherapy with or without anthracyclines. In 1995 we introduced fludarabine, initially as salvage therapy and, since 2001, also as first-line therapy. Since 1990, we have commonly given intravenous immunoglobulin prophylaxis (250-400 mg/kg/every three weeks) for all patients with IgG levels < 400 mg/dL and a history of severe recurrent bacterial infections. Patients who receive fludarabine are given prophylaxis against herpes virus infections with acyclovir (400 mg twice a day) and against *Pneumocystis carinii* and *Listeria monocytogenes* with cotrimoxazole (800mg, three times a week). We defined *fever of undetermined origin* (FUO) as any febrile episodes of mild severity, with a clinical picture compatible with, although not proven, an infective etiology. We defined *documented infection* as any episode with microbiological documentation or with an evident clinical picture consistent to infection. Within the documented infections we defined those episodes requiring hospitalization and/or intravenous anti-infective therapy as *severe*.

In order to determine the association between risk factors (at time of infection) and the severity of infections, a series of logistic models (both univariate and multivariate) was fitted. Huber-White robust standard errors were calculated in order to account for intra-patient correlation of infectious episodes. Stata 8 software (Statacorp, College Station, TX, USA) was used for computations.

Table 1 shows the prevalence of febrile episodes and infections and type and site of documented infections. The incidence of patients with severe infections among

Table 1. Prevalence of febrile episodes and infections, type and site of documented infections.

Total number of patients	379
Male	209
Female	170
Median age in years (range)	68 (34-89)
Median follow up in months (range)	33 (1-203)
Number of patients with febrile episodes	128 (33.7%)
Male	79
Female	49
Median number of episodes for each patient (range)	2 (1-13)
Number of febrile episodes	341
F.U.O and moderate infections	259 (76%)
Severe infection	82 (24%)

	Moderate infections	*Severe infections*	*All*
Bacterial	113 (67%)	72 (88%)	185 (74%)
Viral	43 (25%)	5 (6%)	48 (19%)
Fungal	12 (7%)	2 (3%)	14 (7%)
Mycobacterial	0	3 (4%)	3 (1%)
Protozoal	1(1%)	0	1(0.3%)
Total	169	82	251

Type and site of moderate infections	*N. of infectious episodes (%)*	*Type and site of severe infections*	*N. of infectious episodes (%)*
FUO	90 (35%)	Pneumonia	58 (71%)
Bronchitis	69 (25%)	Sepsis	11 (13%)
Genitourinary	28 (11%)	Scarlet fever	1 (1%)
Herpes Simplex	16 (6%)	Uveitis	1 (1%)
Herpes Zoster	27 (10%)	Tuberculosis	3 (4%)
Rhinitis-Pharyngitis-Sinusitis- Ear infections	7 (3%)	Deep fungal infection	2 (2%)
Oral infections	5 (2%)	Severe Herpes Zoster	3 (4%)
Candida	8 (3%)	Severe Herpes Simplex	1 (1%)
Soft tissue abscess	3 (1%)	Leukoencephalopathy	1 (1%)
Dermatitis	3 (1%)	Meningitis	1 (1%)
Nail infections	1 (0.3%)		
Enteritis	1 (0.3%)		
Intestinal parasitic infection	1 (0.3%)		
Total	259	**Total**	82

Table 2. Risk factors for severe infections: univariate logistic model.

Variable	*Moderate infection and FUO N=259*	*Severe infection N=82*	*OR (95%CI)*	*p value*
Age in years (SD)*	66.1 (9.2)	67.6 (10.7)	1.02 (0.98-1.05)	0.324
Male	58 (59.2%)	21 (70.0%)	1.20 (0.60-2.40)	0.603
Time from diagnosis > 4 yrs	99 (41.1%)	35 (46.0%)	1.22 (0.67-2.22)	0.505
Hypogammaglobulinemia	127 (59.1%)	43 (64.2%)	1.24 (0.64-2.42)	0.525
Treated with fludarabine	42(16.2%)	15 (18.3%)	1.16 (0.50-2.65)	0.730
Neutropenia	10 (6.5%)	2 (4.0%)	0.60 (0.12-2.94)	0.525
More than one line of chemotherapy	31 (12.0%)	24 (29.3%)	3.04 (1.63-5.67)	0.0005
Previous infectious episodes				0.646
no	97 (37.4%)	31 (32.8%)	–	
1-2	95 (36.7%)	26 (31.7%)	0.86 (0.50-1.46)	0.567
>2	67 (25.9%)	25 (30.5%)	1.17 (0.57-2.40)	0.674
Binet stage				0.506
A	57 (22.0%)	13 (16.2%)	–	
B	99 (38.2%)	29 (36.2%)	1.28 (0.55-2.99)	0.562
C	103 (39.8%)	38 (47.5 %)	1.62 (0.69-3.38)	0.266

Statistical units for descriptive statistics are infective episodes for all variables except sex for which the number of patients is reported.

those with febrile episodes was 7 per 100 person year (95% confidence interval: 5.0-11.1). Positive cultures were rare and the most frequently isolated bacteria were *E. coli* and pneumococci. Herpes viruses were frequent, but rarely caused severe infections and never death. We found a few severe opportunistic infections (five episodes), usually in patients with multiple risk factors, such as treatments including fludarabine, hypogammaglobulinemia or advanced stage of disease. Associations between risk factors recorded at the time of infection aand the severity of the infection were searched for by univariate analysis (Table 2). In our experience, fludarabine treatment (previous or current) and prophylaxis with acyclovir and cotrimoxazole, even if involved in the pathogenesis of opportunistic infections, were not associated *per se* with development of severe infections.

Similarly, neutropenia was not found to be a significant risk factor, although in a prospective surveillance study more than 50% of the cases of nosocomial bacteremia in CLL patients occurred with neutrophils $<0.1\times10^9$/L.[10] Only patients submitted to more than one regimen of chemotherapy developed a significantly higher proportion of severe infections. This result was also confirmed by multivariate analysis (odds ratio of the same magnitude as that in univariate analysis: OR= 3.25 95% CI: 1.61-6.55, p=0.001). Our result is similar to that recently reported by Hensel *et al.*[9] who described a series of 187 patients, in whom only disease aggressiveness and previous lines of therapy proved to be major risk factors for infections at multivariate analysis.

Until now it has been debatable whether and when antibacterial prophylaxis could be useful in CLL patients, particularly during the neutropenic period. It is a current strategy to administer antibacterial prophylaxis to CLL patients with previous severe and/or relapsing bacterial infections. Even with all the limits of a retrospective study, our data suggest that patients submitted to more than one line of chemotherapy may run the risk of severe infections, indicating the possible utility of antibacterial prophylaxis also in this subset of patients, and not only in severely neutropenic patients or in those previously affected by severe bacterial infections. Prospective studies are warranted to confirm this point.

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Multiple Myeloma

Bone marrow plasma cell microaggregates detected by immunohistology predict earlier relapse in patients with minimal disease after high-dose therapy for myeloma

Plasma cell microaggregates detected by CD138 immunohistology were demonstrated in 22% of patients achieving morphologic remission 3 months after high-dose therapy for myeloma. Microaggregates were predictive of earlier disease progression, indicating that immunohistology may represent a useful tool in the assessment of minimal disease in patients after high-dose therapy for myeloma.

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The treatment of chemoresponsive plasma cell myeloma with high-dose chemotherapy and autologous stem cell replacement achieves complete response (CR) in one-third of patients.[1] CR requires the sustained absence of serum and urine paraprotein for at least 6 weeks, together with less than 5% plasma cells in the bone marrow as assessed by morphologic analysis.[2] Estimation of plasma cell infiltrates in marrow aspirates and hematoxylin and eosin-stained trephine sections can be subjective and dependent on observer expertise.[3] Immunohistological staining of plasma cells using highly specific antibodies (e.g anti-CD138/syndecan-1) enhances the detection of small plasma cell clusters, or *microaggregates* in the bone marrow (Figure 1A). Microaggregates have been defined as focal and contiguous interstitial collections of at least 10 plasma cells in a non-perivascular location.[4]

In a preliminary analysis, interstitial plasma cell microaggregates were detected in 100% of patients with asymptomatic myeloma (with 10-15% plasma cells in the bone marrow; n=21), in 25% with monoclonal gammopathy of undetermined significance (n=32) and in none of the patients with non-malignant plasmacytosis (n=11). As interstitial plasma cell microaggregates were always present in patients with myeloma, we hypothesized that their presence might be a useful indicator of disease after treatment, particularly in patients fulfilling the criteria for complete morphologic remission (<5%