of MGUS. Furthermore we have confirmed a previously reported correlation[10] between Tc^{99}-MIBI scanning results and laboratory data: β-2-microglobulin, C-reactive protein and lactate dehydrogenase. It would be incorrect to do a Cox-regression test in this small series to check whether these variables are independent of Tc^{99}-MIBI. Further studies should be done to establish the utility of Tc^{99}-MIBI in prognosis, staging and response to therapy in MM.

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Key words: multiple myeloma monoclonal gammopathy, prognosis, M protein, technetium Tc^{99} Sestamibi, radionucelide imaging.

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Chronic Lymphocytic Leukemia

Low-dose intravenous alemtuzumab therapy in pretreated patients affected by chronic lymphocytic leukemia. A single center experience

We report the efficacy and safety of intravenous low-dose alemtuzumab (10 mg three times weekly for 10 weeks) in 12 patients with relapsed or refractory chronic lymphocytic leukemia. Low-dose alemtuzumab induced significant responses in these patients (16% complete remission, 25% partial remission), with mild hematologic and extrahematologic side effects and a low rate of infections, even in the presence of long-lasting severe immunosuppression.

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Several studies have reported the efficacy of standard-dose alemtuzumab (30 mg three times weekly, administered by either the intravenous or the subcutaneous route) in previously treated patients with chronic lymphocytic leukemia (CLL), with overall response rates (ORR) ranging from 33% to 42%.[1-3] Although the response rates were high, standard dose alemtuzumab in refractory patients was associated with considerable hematologic and extrahematologic toxicity.[4,5]

Recently, a pilot study with low-dose subcutaneous alemtuzumab (10 mg three times weekly for 18 weeks) in refractory CLL patients showed a high response rate (ORR: 50%) and a favorable toxicity profile.[6] We therefore administered low-dose alemtuzumab to 12 patients with pretreated CLL. We evaluated the efficacy (NCIWG criteria) of the treatment, the duration of response, the overall survival, the safety, the incidence of infectious complications and the immune recovery. All patients had been previously treated with at least two lines of chemotherapy (range 2-5). In four patients treatment with fludarabine was not attempted because of autoimmune hemolytic anemia or refusal. The median time from the last treatment to initiation of alemtuzumab therapy was 4 months (range 2-24 months) (Table 1).

Alemtuzumab was given intravenously at a dose of 3 mg on day 1; from day 3 the target dose was raised to 10 mg three times weekly for 30 administrations. Treatment was stopped if disease progressed or grade IV thrombocytopenia, infections or cytomegalovirus (CMV) reactivation occurred. Therapy was withheld if the neutrophil count fell below 500/μL, although granulocyte colony-stimulating factor was administered for grade IV neutropenia. CMV screening was conducted by weekly analysis of antigenemia and CMV DNA. Immunological subsets ($CD3^+$, $CD4^+$, $CD8^+$, CD16/56, $CD19^+$) were studied before and after the end of treatment on days 60, 120, 180 and 240. Of the 12 patients, two (16%) obtained a CR and three (25%) achieved a PR, with an ORR of 41% (Table 2). The ORR was 83% in stage A/progressive or B/II disease compared to 0% in stage C/IV disease (p=0.01). The ORR was 50% in patients with mutated V_H genes and 29% in patients with unmutated V_H genes (p=ns). However, both CR were achieved in patients with mutated V_H genes and minimal residual disease was not detectable in these two patients. Five patients who were refractory to previous chemotherapy did not achieve any response to alemtuzumab. The

Table 1. Patients' characteristics.

UPN	Age/Sex	Previous Treatment	Stage at time of alemtuzumab treatment (Binet/Rai)	Ig-VH mutational status	FISH Karyotype	Lymphocytes/ m^3	BM Lymphocytes
1	51/m	CHOP, CTX , APBSCT*	B/II	U	Normal	36000	80%
2	62/m	CHL, COP, FLU	B/II	n.d.	Normal	16400	67%
3	61/f	FLU, RITUX	B/II	M	Normal	56830	70%
4	56/m	CHL,FLU, Splenectomy	C/IV	M	Normal	55100	75%
5	72/f	CHL, CTX	A/progressive	U	Normal	39570	82%
6	56/m	CHL, FLU, CHOP	B/II	U	Normal	50490	36%
7	57/m	FLU, CTX, APBSCT, RITUX, CHOP	C/IV	U	n.e.	1070	90%
8	50/f	FLU, CTX	B/II	M	Del 13q14	32390	86%
9	74/f	CHOP, CHL	C/IV	M	Del 13q14 Del 17p	58470	85%
10	78/m	CHL, COP, FLU	C/IV	U	Normal	67280	77%
11	70/m	CHL, CHOP, FLU, RITUX, RT,	C/IV	U	Del 11q22	148640	90%
12	68/m	CHOP, COP*	C/IV	U	Del 17p	10860	46%

*CHL: chlorambucil; FLU: fludarabine; CTX: cyclophophamide; RITUX: rituximab; RT: radiotherapy; U: unmutated; M: mutated; n.e.: not evaluable; n.d.: not done; *AIHA.*

Table 2. Response to therapy two months after alemtuzumab.

UPN	Total dose of alemtuzumab mg	Response to therapy	Lymphocytes m^3	BM Lymphocytes	Months of follow-up (relapse-months)	Status
1	300	PR	430	10%	+24 (5th)	Live in PD
2	300	PR	470	7%	12 (never)	Died in PR for unknown pneumonia
3	300	CR	940	3%	+15 (n.a.)	Live in CR without MRD
4	300	PD	2230	60%	5 (n.a.)	Died in PD
5	300	PR	1900	n.v.	+11(never)	Live in PR
6	300	SD	2220	15%	+14 (5th)	Live in PD
7	300	PD	390	81%	+14 (n.a.)	Live in PD
8	300	CR	480	5%	+10 (never)	Live in CR without MRD
9	300	SD	1730	n.d.	12 (8th)	Live in PD
10	300	SD	3730	72%	12 (n.a.)	Live in SD
11	130	PD	11280	55%	12 (n.a.)	Died (Richter's disease)
12	300	SD	9280	40%	10 (4th)	Live in PD

median response duration was 10 months (range, 5 to 15+) (Table 2).

Two patients developed grade IV neutropenia. Three patients had grade III anemia, but only one required a single blood transfusion. The other two patients became transfusion-independent during alemtuzumab therapy. Grade III thrombocytopenia was observed in only 1 patient. Non-hematologic *first-dose* side effects were mild in all patients, grade II fever was seen in two patients, whereas all other toxicities were of grade I. No episodes of febrile neutropenia or bacterial infection occurred during treatment. The incidence of CMV reactivation during alemtuzumab therapy was 66%, but no evidence of CMV disease was found.[6] Immunological recovery was markedly delayed during and after alemtuzumab therapy, with a prominent reduction in the T-cell compartment.[7] These data are similar to those of Lundin, who used a higher median cumulative dose (1362 mg), confirming that the immune recovery is dose independent.[8]

Our study demonstrates an ORR of 41% for intravenous low-dose alemtuzumab in previously pretreated CLL patients, which is identical to the ORR observed with standard-dose alemtuzumab. The median response duration was 10 months in patients who achieved CR or PR. The median survival was 13 months (range 5-24+) for all patients and 15 months for responders (range 11-24+), which is also comparable to the results obtained by Keating *et al.*[2] However, in the study by Keating the patients had been more heavily pretreated, especially with fludarabine, and a better response rate was observed in the refractory group. In our series the best responses were observed in patients with relapsed CLL, A-progressive/B-II stage and/or mutated-IgVH genes. Low-dose alemtuzumab was well tolerated with mild hematologic and extrahematologic toxicity. We did not observe any infectious complications except for CMV reactivation, while the incidence of such complications in patients receiving the standard-dose has been reported to range from 26.8% to 33%.[1-3] Results similar to ours were recently reported by Cortellezzi *et al.*, who used the same alemtuzumab dose and schedule but a different route of administration.[9] In conclusion, our data

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