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Malignant Lymphomas

Preliminary observations of a phase II study of reduced-dose alemtuzumab treatment in patients with pretreated T-cell lymphoma

We assessed the impact of a reduced-dose (10 mg × 3/week for 4 weeks) schedule of alemtuzumab in 10 patients with pretreated cutaneous/peripheral T-cell lymphomas. The overall response rate was 60% (2 complete responses and 4 partial responses). In terms of infectious toxicity, cytomegalovirus reactivation occurred in 1 (10%) patient.

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The natural history of peripheral T-cell lymphomas (PTCL) seems to be unaffected by the use of conventional or high-dose chemotherapy, and 5-year overall survival rates remain between 20-40%.[1-4] Recently, alemtuzumab (MabCampath), a humanized anti-CD52 monoclonal antibody, has been reported to induce remission in patients with cutaneous T-cell lymphoma[5] and with PTCLU (unspecified)[6] using conventional dosage schedules. Our study population comprised patients with pretreated PTCLU or mycosis fungoides (MF) treated between March 2003 and March 2004 satisfying these eligibility criteria: histologic diagnosis according to the REAL classification;[7] relapsed/refractory disease after at least two treatments; good performance status; age >18 years; normal renal, hepatic and cardiac function. The protocol was approved by the local Ethical Committee, and informed consent was obtained from all patients.

Alemtuzumab (Schering AG, Milan, Italy) was diluted in 100 mL of 0.9% normal saline and administered over 2 h as an intravenous infusion through a line containing a 0.22 µm filter. An escalating initial dosage regimen was used: 3 mg on day 1; 10 mg on day 3; followed by 10 mg, 3 times a week, for a maximum of 4 weeks. Patients received oral paracetamol, antihistamines, and betamethasone before each alemtuzumab infusion. Trimethoprim/sulphamethoxazole (twice daily, 2 times per week) and valaciclovir (500 mg twice daily) were administered from day 2 until at least 2 months after alemtuzumab discontinuation.

Polymerase chain reaction (PCR) analysis for cytomegalovirus (CMV) was performed until 2 months after discontinuation of alemtuzumab. Responses were evaluated according to International Workshop criteria.[8] All toxicities were assessed using WHO criteria.

Ten patients (8 males, 2 females; median age 65 years, range 49-76) satisfied the eligibility criteria. Of these, 6 had nodal PTCLU and 4 had MF. All MF patients were in stage T3 or T4, N0, M0 of the TNM classification.[9] All PTCLU patients were in stage III-IV according to the Ann Arbor system[10] (Table 1). Among PTCLU patients, 4 presented ≥4 involved nodal sites and 3 had ≥3 involved nodal sites with bulky disease. The median number of prior treatments was 3 (range, 2-4), and the median time from original diagnosis was 13 months (range, 6-15). The overall response rate (ORR) was 60%, with 2 (20%) patients achieving complete responses (CR), and with 4 (40%) obtaining partial response (PR). In the MF subset, the best response was PR (3/4, 75%). However, in the PTCLU subset, there were 2 (33%) CR which lasted 3 and 8 months as well as 1 (17%) PR. The median duration of response was 7 months

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Table 1. Patients' characteristics at entry into the study.

Total number	*10*
Mean age, yrs. (range)	65 (49-76)
Sex M/F	8/2
Histology	
MF	4
PTCLU	6
Stage	
MF	2 T3,N0,M0; 2 T4,N0,M0
PTCL	4 III; 2 IV

Table 2. Previous treatment regimens and lymphocyte count recovery after alemtuzumab.

Case no. Diagnosis	*Previous therapy*	*Time to ≤0.1×10⁹/L lymphocytes*	*Recovery time of lymphocytes ≥1×10⁹/L (from the end of alemtuzumab)*
1, MF	PUVA, IFN, Gemcitabine,	Week 2 of treatment	12 weeks
2, MF	PUVA, RT, IFN, Gemcitabine	Week 2 of treatment	5 weeks
3, MF	PUVA, CVP, Gemcitabine	Week 2 of treatment	13 weeks
4, MF	PUVA, CHOP, Gemcitabine	Week 3 of treatment	26 weeks
5, PTCLU	VNCOP-B, CVP, RT	Week 2 of treatment	4 weeks
6, PTCLU	VNCOP-B,RT, Gemcitabine	Week 3 of treatment	12 weeks
7, PTCLU	CHOP,RT, VNCOP-B	Week 3 of treatment	20 weeks
8, PTCLU	CHOP, IEV, RT, CVP	Week 3 of treatment	8 weeks
9, PTCLU	VNCOP-B, RT, Oxaliplatin	Week 3 of treatment	12 weeks
10, PTCLU	CHOP, RT, Oxaliplatin	Week 3 of treatment	13 weeks

(range, 2-10 months). Table 2 summarizes the previous treatments and the lymphocyte reconstitution post-treatment for each patient. Alemtuzumab was well tolerated. Infusion-related adverse events were reported in 3 patients: shivers/chills during the first week (n=2) and hypotension (n=1). Concerning hematologic toxicity, no grade 3-4 anemia/neutropenia/thrombocytopenia was observed. CMV reactivation occurred in only 1 patient (at 1 week after the end of treatment): this patient presented only fever and was treated with ganciclovir, which resolved the infection. There were no other infections.

Alemtuzumab has been shown to be active in MF[5] and PTCL,[6] but with an associated risk of major hematologic toxicity and infectious complications. In this pilot study we found that a reduced dose schedule of alemtuzumab could effectively induce response while apparently avoiding life-threatening side effects. Our encouraging response rates are broadly in line with those achieved by Lundin *et al*.[5] and Enblad *et al*.[6] in pretreated MF and PTCL patients, respectively, utilizing conventional alemtuzumab schedules. However, our results were obtained with just one third of the conventional dose (10 mg instead of 30 mg, 3 times/week), administered for only 4 (instead of 12) weeks. Despite this dose reduction, we observed a 50% ORR among our PTCLU patients as compared with 40% in the PTCLU subset reported by Enblad *et al*.[6] The 75% ORR (albeit without CR) among our 4 MF patients also seems encouraging alongside data reported by Lundin *et al*.,[5] who reached a 55% ORR with the conventional schedule. Our schedule appeared to be better tolerated in terms of toxicity. None of our patients suffered grade 3–4 hematologic toxicity, whereas Enblad *et al*.[6] reported several treatment-related deaths. Furthermore, CMV reactivation was recorded in only 1 (10%) of our patients, as compared with 42% of the patients treated by Enblad *et al.*[6]

In conclusion, this pilot study provides further evidence that alemtuzumab can effectively exert strong antitumor activity in patients with MF/PTCLU and, more importantly, alemtuzumab at lower doses increases safety while maintaining effectiveness.

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Key words: CTCL, PTCL, alemtuzumab, low-dose.

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