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Alemtuzumab (Campath-1H)

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Monoclonal antibodies (MoAb) augment the host anti-tumor response by selectively targeting the malignant cells. MoAb can mediate anti-tumor effects through three major mechanisms including intrinsic cytotoxic activity, antibody-dependent cellular cytotoxicity (ADCC), and activation of complement-dependent cytolysis. Alemtuzumab is a humanized IgG1 MoAb that targets the glycosylated peptide cell surface antigen CD52 that is abundantly expressed (approximately 500,000 molecules/cell) on normal and malignant B- and T-cells, but not on hematopoietic stem cells. It was approved by the US Food and Drug Administration (FDA) in 2001 for the treatment of refractory B-cell chronic lymphocytic leukemia (B-CLL). There have been several anecdotal reports of alemtuzumab activity in cutaneous T-cell lymphomas (CTCL).[1] Meaningful durable clinical responses were witnessed with acceptable toxicity. These observations have led to the initiation of more formalized phase II evaluations.

Lundin and colleagues reported the results of their phase II study of alemtuzumab in twenty two patients with advanced mycosis fungoides/Sézary syndrome (MF/SS).[2] This was an open-label study conducted in 8 European centers in patients with MF/SS, clinical stage II to IV who did not respond adequately to treatment with at least PUVA, radiotherapy, or systemic chemotherapy. All patients had strong CD52 expression on the malignant T-cells. Alemtuzumab was administered intravenously in this study. The first dose was 3 mg, which was increased to 10 mg and then to 30 mg as soon as infusion-related reactions were tolerated. The 30 mg dose was subsequently administered 3 times a week for up to 12 weeks. Concomitant treatment included paracetamol and the antihistamine clemastine prior to the initial infusions. The use of corticosteroids as secondary prophylaxis during week 1 in case of flu-like first-dose reactions was optional. Patients also received prophylaxis with cotrimoxazole and valacyclovir. Allopurinol was taken from day 1 to day 28.

The median age of the patient population was 61 years (range 38-77). Clinical stage included IIA (5%), IIB (9%), IIIA (27%), IIIB (18%), and IVA (32%). On study WHO performance status was 0 (22%), 1 (55%), and 2 (23%). B-symptoms were present in 36% of patients. Seventeen patients noted pruritus. The median number of previous treatment regimens was 3 (range 1-10). The overall response rate was 55%, with 32% of patients in complete remission and 23% in partial remission. Sézary cells were cleared from the blood in 6 of 7 (86%) patients, and regression of adenopathy was observed in 6 of 11 (55%) patients. Higher response rates were seen in erythrodermic patients (overall response rate [ORR], 69%), than in patients with plaque or skin tumors (ORR, 40%). Patients with fewer previous treatment regimens (1 or 2) had a higher response rate than in those who had received 3 or more regimens (ORR 80% vs. 33%). A significant impact on pruritus was noted. The median time to treatment failure was 12 months (range, 5-32+ months). A spectrum of side effects was witnessed with alemtuzumab therapy. All patients developed lymphopenia. Cytomegalovirus (CMV) reactivation (causing fever without pneumonitis and responding to ganciclovir) occurred in 4 (18%) patients. An additional six patients had suspect or manifest infection (fever of unknown origin 3; generalized herpes simplex 1; fatal aspergillosis 1). One patient had a fatal *Mycobacterium pneu-*

Table 1. Patient characteristics at baseline (n=19).

Age (years)	
Median (range)	63 (39-88)
Gender	
Male	9
Female	10
TNM stage	
PD	
III	8 (42%)
IVA	10 (53%)
IVB	1 (5%)
No. prior treatments	
Median (range)	5 (2-10)

Table 2. Results of treatment (n=19).

Follow-up (months)	
Median (range)	18 (1-50)
Best response	
CR	9 (47%)
PR	6 (32%)
PD	4 (21%)
8 (42%)	
Response duration (months)	
Median (range)	6 (1-37)
Survival time (months)	
Median	18 (1-50)
Current status	
Alive	9
Dead	10

Table 3. Toxicities associated with alemtuzumab (n=19).

Side effect	*NCI Toxicity Grade (vs 3.0)*			
	I	II	III	IV
Anemia	1	4	1	1
Leukopenia		8	4	1
Neutropenia		1		
Thrombopenia	1		4	1
Constitutional symptoms				
Pruritus/pain		10		
Fatigue		2		
Chills		2		
Fever		1		
Rigor	1	4		
Sweats		1		
Infection		2	3	
Skin		9		1
Alopecia		1		
Allergy/urticaria		2		
Edema		2		
Hyperkalemia				1
Dyspnea/SOB		3		
Neurological		3		
Hypertension		1		
Gastrointestinal				
Nausea/vomiting		2		
Anorexia		3		
GI obtruction				1
Urinary retention			3	

monia at 10+ months. All serious infectious adverse events (except CMV) occurred in patients who had received 3 or more prior regimens. One single patient had progression of a cutaneous squamous cell cancer. Hematologic toxicity included transient grade 4 neutropenia in 4 (18%) patients after a median time of 11 weeks (range, 8-12). One (5%) patient acquired transient grade 4 thrombocytopenia. Patients with grade 4 cytopenias recovered spontaneously during continued alemtuzumab treatment or after the end of the treatment period.

Kennedy and colleagues have also published their results on a cohort of advanced MF/SS patients treated with alemtuzumab.[3] A total of eight patients with relapsed or refractory disease were included in their report. The median age was 48 years (range, 30-62). The stage at time of alemtuzumab therapy was IIB (5), IIIB (2) and IVB (1). Disease duration ranged from 13-87 months. Six patients had MF and two SS. All patients had been exposed to a number of previous treatments. Alemtuzumab was dose-escalated to 30 mg intravenously 3 times a week. The median treatment duration was 6 weeks (range, 2-13). Concomitant medications included paracetamol, metoclopromide and lorazepam prior to infusion. Prophylactic cotrimoxazole, fluconazole or itraconazole, and acyclovir or valacyclovir were given during treatment and continued for an additional two months. The ORR was 38% with 3 partial responders. All 3 patients developed progressive disease (PD) within 4 months of starting alemtuzumab. The reasons for withdrawal were disease progression (four patients), infectious complications (two patients with CMV and Parvovirus, respectively), infusion-related side effects (one patient), and completion of therapy (one patient). Lymphopenia was a universal consequence of treatment. Additional infectious complications included methicillin resistant *Staphylococcus aureus* (MRSA) skin and line infections, viral bronchitis, cutaneous varicella-zoster infection, oral *Herpes simplex* type 1 infection, *Pseudomonas osteomyelitis*, and *Klebsiella sepsis*. Hematologic toxicity was NCI grade 2-3 anemia 25%, grade 4 anemia 12%; grade 2-3 neutropenia 25%; grade 4 neutropenia 38%; and grade 2-3 thrombocytopenia 12%, grade 4 thrombocytopenia 38%. The Northwestern Multidisciplinary CTCL Group has an extensive experience with the clinical use of alemtuzumab in erythrodermic CTCL. Currently, there is an ongoing

clinical phase II trial with alemtuzumab for advanced stages of MF/SS. Preliminary results of this ongoing phase II trial and the clinical use of alemtuzumab in patients with advanced MF/SS showed promising efficacy particularly in patients with erythrodermic CTCL. Alemtuzumab was intravenously administered at a dose of 30 mg three times per week for 4 weeks followed by subcutaneous administration for additional 8 weeks with unchanging dosage and schedule. Nineteen patients with erythrodermic MF or SS have been treated to date. Fifteen patients have been enrolled into the study and 4 patients who did not meet the prestudy criteria were treated off study. Patient age at presentation ranged from 39 to 88 years, with a median age of 63 years. Clinical stages were: 8 (42%) stage III; 10 (53%) stage IVA; 1 (5%) stage IVB. All patients were heavily pretreated with a median of 5 prior treatments. The ORR was 79% (15 patients) with CR in 47% (9) of patients and PR in 32% (6) of patients clearing effectively circulating Sézary cells. Four patients (21%) developed PD with the development of cutaneous tumors in one patient despite complete clearing of circulating Sézary cells. Median response duration was 6 months (range, 1-37 months). The median overall survival of all patients was 18 months (range, 1-50 months). Ten patients (53%) have died, 7 (37%) attributable to MF. In general, treatment was well tolerated, with the majority of toxicities being Grade 2 in severity and transient. The most frequent toxicities included hematologic toxicities and constitutional symptoms. Infectious complications occurred in 5 patients (grade 2 or 3). Almost all patients developed grade 4 lymphopenia. Five patients developed grade 3 or 4 leukopenia with pancytopenia in 2 patients requiring withholding and/or discontinuation from treatment. Common cytopenias and prolonged immunosuppression required long-term prophylactic treatment with trimethoprim-sulfamethoxazole, acyclovir, and diflucan.

References

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