Chronic Lymphoid Leukemia

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Safety and efficacy of subcutaneous Campath-1H for treating residual disease in patients with chronic lymphocytic leukemia responding to fludarabine

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Background and Objectives. Recent observations suggested that targeted monoclonal antibodies might be best employed in lymphoid malignancies under conditions of minimal residual disease. This prompted us to investigate the role of Campath-1H as treatment for patients with chronic lymphocytic leukemia (CLL) in whom fludarabine (FAMP) had produced a marked disease debulking with persistence of bone marrow (BM) infiltration or a complete remission (CR) without the disappearance of the molecular aberration (IgH monoclonal expression). As intravenous Campath-1H is almost invariably associated with reactions, sometimes of WHO grade 3-4, we adopted the subcutaneous route of administration, which proved to induce rare and mild adverse reactions but had comparable efficacy.

Design and Methods. Nine patients (7 males, 2 females) with a median age of 55 years (range 41-61) who responded to FAMP (1 had a CR, 5 a nodular partial remission [PRN], and 3 a partial remission [PR]), according to NCI Working Group Criteria, received subcutaneous Campath-1H, three times a week for 6 weeks in escalating doses up to 10 mg. Monoclonal rearrangement of IgH was present in all patients before immunotherapy. Patients received acyclovir and cotrimoxazole as infection prophylaxis. Granulocyte colony-stimulating factor (G-CSF), at the dosage of 5-10 μg/kg/die, or intermediate-dose Ara-C (800 mg/m²/q 12h × 6 doses), was administered to obtain peripheral blood stem cell (PBSC) mobilization.

Results. All patients were evaluable for response. Five patients, 2 in PR and 3 in PRN after FAMP treatment, reached a CR. Three patients, one in PR, one in PRN and one in CR, converted to a molecular remission. In four out of seven patients PBSC harvesting was successful; more than 2.5×10^6 cells/kg were collected from all these patients. Collection was polyclonal for IgH gene rearrangement in three cases. One patient has been transplanted after cyclophosphamide and total body irradiation as conditioning regimen, without complications and with rapid hemopoietic engraftment. All patients were evaluable for toxicity. A WHO grade 1-2 skin reaction was observed in 5 patients at the site of injection. No infectious episodes were recorded. Two out of three patients presenting cytomegalovirus reactivation, without pneumonia, were successfully treated with oral gancyclovir.

Interpretation and Conclusions. Subcutaneous Campath-1H administered to CLL patients with residual BM disease after FAMP proved to be safe and effective. Of nine patients, three obtained a molecular CR and five converted into a morphologic and immunophenotypic CR. In four of seven patients submitted to PBSC mobilization, this treatment also allowed a harvest uncontaminated by CD5/CD19 double-positive CLL cells, which was polyclonal for IgH gene rearrangement in three cases.

Key words: Campath-1H, fludarabine, chronic lymphocytic leukemia.

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The introduction of chemotherapeutic agents such as fludarabine (FAMP) has made it possible to treat chronic lymphocytic leukemia (CLL) more effectively than was previously possible using alkylating agents. Even if more than 30% of untreated patients obtain complete remission (CR) the majority of them relapse after a median time of 20 to 30 months.[1,2] Different strategies are under investigation to reach at least longer duration of response. High-dose chemotherapy with autologous hematopoietic stem cell support may be a suitable option. Contamination of bone marrow (BM) and peripheral blood (PB) by residual leukemic cells may preclude the success of this procedure. Targeted monoclonal antibodies offer a promising alternative to chemotherapy in refractory CLL. Among such antibodies, two have emerged with some promise: rituximab, a chimeric humanized anti-CD20, and alemtuzumab (Cam-

path-1H), a humanized anti-CD52 antibody. CD52 is an antigen expressed at high levels on most normal and malignant mature lymphocytes but not on hematopoietic stem cells.[3,4] Campath 1-H is the genetically reshaped human IgG1 antibody directed against CD52. The mechanism to lyse cells showed that both antibody-dependant cellular cytotoxicity (ADCC) and complement binding are necessary.[5] Although this antibody is consistently effective against malignant lymphocytes in blood, marrow and spleen, it is much less effective against cells in lymph nodes and extranodal masses. Most of the published studies reported results in heavily pre-treated patients,[6] resistant to fludarabine.[7,8] Recent observations suggesting that antibodies might be best employed under conditions of minimal residual disease[9,10] prompted us to investigate the possible role of subcutaneous Campath-1H in patients with CLL in whom FAMP had produced a marked disease debulking, with persistence of BM leukemic infiltration precluding stem cell harvest and autologous transplantation.

Another issue of our study regards the route of administration of Campath-1H. Intravenous administration is almost invariably associated with reactions consisting of fever, rigors and nausea, due to the release of cytokines such as tumor necrosis factor α and interleukin-6, that are more frequent and sometimes of grade 3-4 after the early days of administration. The subcutaneous route of administration may, therefore, be the preferred because adverse reactions are very rare and mild.[11]

The aims of this study were: a) to define the role of alemtuzumab as treatment of residual disease after fludarabine; b) to demonstrate the feasibility of collection of PB stem cells and the quality of harvest after Campath-1H therapy; c) to assess the safety profile of Campath-1H subcutaneous administration.

Design and Methods

The characteristics of the nine patients treated with Campath-1H are summarized in Table 1. Seven are males and 2 females, with a median age of 55 years (range 41-61). Chemotherapy before Campath-1H consisted of: FAMP as first-line treatment in six cases, FAMP as salvage in two patients showing resistance to chlorambucil plus prednisone, FAMP plus cyclophosphamide (CTX)[12] at disease progression after FAMP therapy in one case. All patients had received at least 3 cycles of FAMP, 25 mg/m^2 iv or 40 mg/m^2 orally for 5 days (range 3-8). Treatment initiation of FAMP required the criteria of active B-CLL according to NCIWG guidelines.[13] The median time from FAMP discontinuation to Campath-1H was 5 months (range 2-11).

Restaging, performed after completion of treatment with the purine analog, immediately before and after Campath-1H, included: bone marrow aspiration, trephine biopsy, immunophenotyping, and molecular study for IgH rearrangement. Immunophenotyping of lymphoid cells co-expressing CD5, CD19, CD 23, CD 79b and FMC7 was done by quadruple color flow cytometry (BD Biosciences, San José, CA, USA) with directly-labeled antibodies[14] on unprocessed whole blood; percentages of CD5/CD19 double positive cells given in the text are a percentage of all lymphoid cells. The quantitative expression of CD52 (Senotec, Oxford, UK) was determined. The polymerase chain reaction (PCR) method for the Ig heavy chain gene used a Fr2 or Fr3 V-region primer in conjunction with nested primers directed to the J region.[15] All patients were submitted to ultrasound of the abdomen and standard radiography of the thorax, while computed tomographic scanning of abdomen and thorax was done only in selected cases.

Response criteria were those defined by the National Cancer Institute (NCI) Working Group[13] CR required the disappearance of all palpable disease, normalization of the blood counts (PMN >1.5×10^9/L, platelets >100×10^9/L, Hb > 11 g/dL), BM aspirate lymphocyte percentage < 30% and no evidence of disease on BM biopsy. A nodular partial remission (PRN) required the same criteria as for CR with the exception that lymphoid nodules could be seen on BM biopsy. A partial remission (PR) required 50% or more reduction in palpable disease as well as one or more of the remaining features: PMN > 1.5×10^9/L or 50% improvement over baseline, platelets > 100×10^9/L or 50% improvement over baseline, and Hb more than 11 g/dL or 50% improvement over baseline without transfusions. No BM evaluation was required for determination of PR.

Treatment

Campath-1H (supplied by Ilex Oncology, Guilford Sussex, UK) was given at least 8 weeks after the discontinuation of FAMP. It was administered subcutaneously, three times a week for 6 weeks, in escalating doses up to 10 mg, with a premedication of 1 g paracetamol and 10 mg of clorphenamine. Patients received acyclovir and cotrimoxazole as prophylaxis from the start of treatment. To obtain a PBSC harvest, G-CSF, 5-10 μg/kg/die, was started 8 weeks after completion of alemtuzumab, and collection was performed when CD34$^+$ cells reached ≥ 10 μL. Patients whose PBSC mobilization with G-CSF failed were planned to undergo a second

Table 1. Characteristics of the 9 patients before treatment.

Pts.	*Age/sex*	*Stage pre Tx RAI/Binet*	*Previous treatment*	*Bone marrow infiltration pre Campath*	*Status before Campath*	*IgH*	*Time from last treatment to Campath*	*Total dose Campath*
1	44/M	IV/C	CLB+PDN FAMP × 6	Aspirate: 20% Trephine: nodular $CD5^+/CD19^{+}$: 5.50%	PRN	monoclonal	8 months	264 mg
						monoclonal	5 months	264 mg
2	57F	I/A	FAMP × 8 (oral)	Aspirate: 20% Trephine: nodular $CD5^+/CD19^{+}$: 10%	PR			
3	41/M	IV/C	FAMP × 6	Aspirate: 40% Trephine: 40% $CD5^+/CD19^{+}$: 46%	PR	monoclonal	6 months	210 mg
4	55/M	IV/C	CLB+PDN FAMP × 5	Aspirate: 40% Trephine: nodular $CD5^+/CD19^{+}$: 11.5%	PRN	monoclonal	2 months	264 mg
5	54/M	II/A	FAMP × 8 (oral)	Aspirate: 5% Trephine: nodular $CD5^+/CD19^{+}$: 3.5%	PRN	monoclonal	5 months	264 mg
6	61/M	IV/C	FAMP × 6	Aspirate: 35% Trephine: nodular $CD5^+/CD19^{+}$: 30.6%	PRN	monoclonal	2 months	264 mg
7	61/M	II/A	FAMP × 6	Aspirate: 10% Trephine: 10% $CD5^+/CD19^{+}$: 2.5%	CR	monoclonal	2 months	264 mg
8	55/M	I/B	FAMP × 6	Aspirate: 10% Trephine: nodular $CD5^+/CD19^{+}$: 30.6%	PRN	monoclonal	2 months	264 mg
9	52/F	II/A	FAMP × 6 FAMP+CTX × 3	Aspirate: 30 % Trephine: 20% $CD5^+/CD19^{+}$: 14%	PR	monoclonal	11 months	264 mg

attempt at harvesting with intermediate-dose Ara-C (ID-Ara-C), 800 mg/m²/q12 h for 6 doses.

Results

Table 1 shows the disease status before FAMP at the start of Campath-1H. Before starting alemtuzumab, one patient was in complete morphologic and immunophenotypic remission, three in PR and five in PRN. Monoclonal rearrangement of IgH was present in all patients. The median follow-up after alemtuzumab is 24 weeks (range 6-44). The first restaging, two to three weeks after Campath-1H discontinuation was performed in all patients. The second restaging has been performed in five patients four months after the first re-evaluation.

As shown in Table 2, two patients in PR after FAMP treatment (#2 and 3) reached CR, both showing a persistent monoclonal rearrangement of the IgH gene. Three patients (#5, 6, and 8) in PRN after FAMP reached a CR without any switch to a polyclonal rearrangement of the IgH gene. Patients #1 and #9 converted from PRN and PR, respectively, to CR showing a polyclonal rearrangement of the IgH gene. Patient #4 (PRN) presented a decrease of bone marrow infiltration from 40% to 10%, but the morphologic pattern of BM showed a persistence of nodules and the patient was reclassified as being in PRN. The only patient in CR after chemotherapy (#7) converted to a polyclonal rearrangement of the IgH gene after immunotherapy.

Seven patients proceeded to PBSC mobilization. This was successful in three cases after the first attempt with G-CSF, while in one patient ID-Ara-C had to be administered after a collection of 1.28×10^6 $CD34^+$ cells/kg with growth factors. All four cases had a final harvest of more than 2.5×10^6 cells/kg, which was considered the minimum for a successful transplantation procedure. Collection was polyclonal for the IgH gene rearrangement in three cases (patients #1, 4 and 7). Patient #1 was transplanted 16 weeks after completion of Campath-1H therapy. He was conditioned with a CTX-TBI protocol, without complications and with rapid hematopoietic engraftment, and was disease-free at the 4-month follow-up.

Side effects

All patients were evaluable for toxicity. A skin reaction in the site of the subcutaneous injection, of grade 1-2 according to the WHO scale, was the most frequent side effect observed. This event

Table 2. Results in the 9 patients after Campath-1H treatment.

Pts.	*age/sex*	*Bone marrow infiltration post Campath*	*IgH rearrangement*	*Status after Campath*	*Time from Campath to stem cell harvest*	*PBSC $CD34^+ \times 10^6$/kg*	*PBSC IgH rearrangemet*	*Follow-up after Campath (weeks)*
1	44/M	Aspirate: 5% Trephine: 5% $CD5^+/CD19^+$: 1%	polyclonal	CR	1 month	3.4	polyclonal	33
2	57F	Aspirate: 5% Trephine: 20% $CD5^+/CD19^+$: 6.2%	monoclonal	CR	2 months	NM	–	32
3	41/M	Aspirate: 10% Trephine: 10% $CD5^+/CD19^+$: 0%	monoclonal	CR	2 months	3.26	monoclonal	44
4	55/M	Aspirate: 10% Trephine: nodular $CD5^+/CD19^+$: 0%	monoclonal	PRN	3 months	1.28 (G-CSF) 27.0 (ID-Ara-C)	polyclonal	32
5	54/M	Aspirate: 5% Trephine: 5% $CD5^+/CD19^+$: 1.5%	monoclonal	CR	2 months	NM	–	24
6	61/M	Aspirate: 10% Trephine: 5% $CD5^+/CD19^+$: 3.5%	monoclonal	CR	2 months	NM	–	12
7	61/M	Aspirate: 5% Trephine: 5% $CD5^+/CD19^+$: 1.5%	polyclonal	CR	2 months	3.2	polyclonal	10
8	55/M	Aspirate: 5 % Trephine: 0% $CD5^+/CD19^+$: 0%	monoclonal	CR	NA	NA	NA	7
9	52/F	Aspirate: 5% Trephine: 5% $CD5^+/CD19^+$: 3%	polyclonal	CR	NA	NA	NA	6

NM: no mobilization; NA: not assessable (too early).

occurred in 5 patients approximately 24 hours after the first injection and persisted until the fourth administration. One of these patients developed a generalized eczema at the end of treatment, which improved after steroids. Two episodes of fever, WHO grade I, were observed in one case after the first two injections. As regards hematologic toxicity, none of the patients developed anemia or thrombocytopenia during treatment. One patient who started treatment with a mild thrombocytopenia (platelets 110,000/μL) showed a progressive increase in platelet numbers until achieving persistent normalization of the platelet count after three weeks of Campath-1H. Two patients developed an episode of grade 2 neutropenia after 4 and 5 weeks of treatment; in both cases G-CSF was administered with a rapid recovery of PMN count.

No infectious episodes occurred during treatment or during a median follow-up of 24 weeks after the discontinuation of Campath-1H. All patients were monitored for CMV reactivation (pp65 antigenemia) weekly, during treatment and for six weeks after drug discontinuation. Three patients demonstrated CMV reactivation at the end of treatment without developing CMV disease. Oral gancyclovir was administered in two cases, in one case because of the presence of symptoms (fever, nausea) and in the other because of the elevated number of positive cells. Antigenemia became negative in all patients, after 2 weeks in two cases and 3 weeks in the last patient.

Discussion

Targeted therapy with monoclonal antibodies of different specificities has been used in lymphoid malignancies.[10] The nature of the target antigen plays an important role in the likelihood of therapeutic success. Antigens such as CD52 and CD20 are non-modulating and their therapeutic efficacy is, therefore, elevated. CD52 is permissive for lysis with both effector cells and complement, so that Campath-1H may be an ideal agent in CLL.

It has been shown that there is a wide range of clinical indications in this setting. Osterborg *et al.*[6] administered Campath-1H, 30 mg over 2 hours intravenously, thrice weekly for a maximum of 12 weeks to 29 heavily pretreated CLL patients. Eleven patients (38%) achieved a PR and 1 (4%) CR for an overall response rate of 42%. In a multicenter phase II clinical trial, 93 CLL patients previously treated

with alkylating agents and refractory to FAMP received Campath-1H, 30 mg over 2 hours intravenously, three times a week for 4-12 weeks.[7] The overall response rate was 33% with 2 (2%) CR and 29 (31%) PR. Campath-1H has also been administered to a small cohort of patients with previously untreated B-CLL,[16] giving a response rate of 89% (8/9 patients, three of them attaining CR). These responses were remarkably stable, being the longest seen in any group of patients treated with Campath-1H. All these data could open a variety of new therapeutic options. In fact, another trial has shown that alemtuzumab may be useful to *purge* residual disease in patients achieving a maximal response with purine analogs.[9] In this study low doses of Campath-1H induced CR in five of six patients with residual disease following either FAMP or deoxycoformycin. This favorable experience prompted us to test Campath-1H systematically as post-remission treatment in patients with CLL.

The policy at our institution towards younger patients with CLL is to treat them with FAMP as first-line treatment, and to submit patients responding to FAMP to $CD34^+$ cell collection and autologous stem cell transplantation. Since early 2001, when Campath-1H became available for treatment, patients achieving PR, PRN and CR but not molecular response with fludarabine, were planned to receive low doses of Campath-1H administered subcutaneously for six weeks before PBSC mobilization, as an attempt at *in vivo* purging.

Three patients obtained a molecular CR (one from CR, one from PRN and one from PR) and five converted to a morphologic and immunophenotypic CR, from a PRN in three cases and from a PR in two. Mobilization of PBPC, attempted in 7 patients, was successful in four of them. One patient in molecular CR yielded a product showing polyclonal rearrangement of IgH. He was transplanted after CTX and TBI as conditioning regimen, without delay of engraftment or infective complications, and was disease-free at four months follow-up. Surprisingly, the only patient showing a stable PRN after Campath-1H, although with a considerable reduction of nodules in the marrow, produced $CD34^+$ cells without any evidence of monoclonality for IgH. Four of seven patients submitted to PBSC mobilization, yielded more than 2.5×10^6 cells/kg, which was considered the minimum for a successful transplantation procedure. A successful harvest was obtained for three of them after G-CSF, and for one after a second attempt with ID- Ara-C.

The second important issue emerging from our study is the choice of the route of administration of Campath-1H. Intravenous administration is almost invariably associated with *first dose* reactions consisting of fever, rigors and nausea. These adverse effects are presumably secondary to transient elevations of the levels of TNF-α, interferon-γ and IL-6 occurring after administration of alemtuzumab.[8,17,18] Only a few papers have reported that the subcutaneous route of administration reduces the intensity of side effects while maintaining the same efficacy.[11,19] Unfortunately, no pharmacokinetics studies on the subcutaneous route of administration have been carried out so far. Our results confirm previous observations on the high efficacy without grade 3-4 WHO toxicity.

Hematologic side effects may also occur. Anemia, neutropenia and thrombocytopenia tend to be transient and moderate, although sometimes profound and long-lasting neutropenia has been described. We did not observe any hematologic grade III-IV toxicity in our patients. The principal concern about Campath-1H is the concomitant reduction of all normal lymphocytes of both B- and T-lineage, resulting in a profound and long-lasting lymphopenia. This has been associated with an increase in opportunistic infections in heavily pretreated patients.[20] All our patients received prophylaxis for PCP and herpes virus infections. We did not observe any opportunistic infection after a median follow up of 24 weeks. CMV reactivation has been reported following treatment with alemtuzumab.[21] The incidence of CMV infection was evaluated in 1538 patients: CMV infections occurred in 3.6%, causing death in 3 cases (2.2%).[22] An antigenemia reactivation was observed in three of our patients. We treated two of them with oral gancyclovir, one because of fever and the other because of high levels of positivity, and none developed overt CMV infection.

In conclusion, the therapeutic activity of Campath-1H was confirmed in CLL patients responsive to FAMP but showing persistence of BM infiltration, and proved capable of eliminating residual disease as demonstrable by flow cytometry and polymerase chain reaction for IgH rearrangement. Longer follow-ups and larger series are required to assess the clinical value of alemtuzumab as a method of *purging* residual CLL disease confined to the blood and bone marrow.

Contributions and Acknowledgments

MM designed the study and wrote the paper. MM, AC, AT, VR, RC, EP were responsible for clinical management of the patients and acquisition of clinical data. BB was responsible for the immunophenotyp-

ing and SV for the molecular studies. MM, AT and EM were involved in critically revising the intellectual content of the manuscript.

Disclosures

Conflict of interest: none.

Redundant publications: no substantial overlapping with previous papers.

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Peer Review Outcomes

Manuscript processing

This manuscript was peer-reviewed by two external referees and by Professor Mario Cazzola, Editor-in-Chief. The final decision to accept this paper for publication was taken jointly by Prof. Cazzola and the Editors. Manuscript received March 14, 2002; accepted May 13, 2002.

What is already known on this topic

Despite fludarabine representing a useful tool in the treatment of chronic lymphocytic leukemia, only a minority of patients achieve long-lasting remissions with this drug. Clearly, there is a need for more effective therapeutic tools. Campath-1H is a humanized antibody anti-CD52, an antigen expressed at high levels on lymphocytes but not on hematopoietic stem cell.

What this study adds

Subcutaneous Campath-1H administered to patients with chronic lymphocytic leukemia showing residual bone marrow disease following fludarabine treatment may be safe and effective.

Potential implications for clinical practice

Subcutaneous Campath-1H may be employed in the treatment of residual disease in selected patients with chronic lymphocytic leukemia.

Mario Cazzola, Editor-in-Chief