Alemtuzumab (Campath-1H) and CHOP chemotherapy as first-line treatment of Peripheral T-cell Lymphoma: results of a GITIL prospective multicenter trial

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ABSTRACT

To evaluate in a prospective multicenter trial the feasibility and clinical efficacy of the combination of alemtuzumab (Campath-1H) with the CHOP regimen (CHOP-C) as the primary treatment for patients with peripheral T-cell lymphoma (PTCL), between January 2003 and December 2005, 24 consecutive PTCL patients entered the study and received 8 CHOP courses, Campath was added at 30 mg. s.c. at day -1 initially to the first four courses (four patients), and then to all eight courses (20 patients). CR was achieved in 17 (71%) patients, 1 had partial remission and 6 stable/progressive disease. At a median follow-up of 16 months (5-42), 14 patients are alive, nine had died from progressive disease and one from pneumonia at day +198 while in CR. So far, 13 are disease-free, with an overall median duration of response of 11 months. The most frequent side effect were grade 4 neutropenia and CMV reactivation. Major infections were J-C virus reactivation, pulmonary invasive aspergillosis, Staphylococcus sepsis and pneumonia. This study shows that CHOP-C: (1) is a feasible chemoimmunotherapy regimen; (2) is effective in PTCL with a high rate of CR achievement and (3) is associated with mostly manageable infectious complications. This clinical trial was registered with the Osservatorio Nazionale sulla Sperimentazione cinica as ID# 141202.
INTRODUCTION

In western countries peripheral T-cell non-Hodgkin lymphomas (PTCL) account for 15%-20% of aggressive lymphomas and for 7% -10% of all the non-Hodgkin lymphomas (NHL). They usually occur in middle to advanced age with a peak incidence between the fifth and sixth decades, presenting as a widespread disease in more than two-thirds of the patients and showing an aggressive behavior, with more than half of the patients dying of their disease within one year. Most authors agree about the comparatively grim prognostic outcome of the a T-cell compared to a B-cell phenotype. The former remains a negative prognostic factor in a multivariate analysis, and appears to be independent from International Prognostic Index (IPI).

The natural history of PTCL seems unaffected by second- and third-generation chemotherapy regimens and the 5-year overall survival still remains between 25% and 47%. However high-dose chemotherapy followed by autologous hematopoietic stem cell transplant (ASCT) has been successfully performed in selected studies mostly for resistant, relapsing disease. Corradini et al. in a cohort of 62 PTCL patients treated with a high-dose sequential program followed by ASCT as front-line therapy definitely demonstrated no benefit of autologous bone marrow transplantation over standard chemotherapy.

CD52 antigen is present on normal and pathological B and T cells with the highest values in T-prolymphocytic leukemia (T-PLL), as shown by Ginaldi et al., using quantitative flow cytometry. In PTCL, however, CD52 expression varies from case to case, with an overall expression rate lower than 50%. Nevertheless, CD52 can be a suitable target for immunotherapy-based programs, given the availability of the anti-CD52 humanized monoclonal antibody alemtuzumab (Campath-1H). Thus, a prospective multicenter clinical trial was designed aimed to explore both the efficacy and the safety of a chemo-
immunotherapy approach based on the combination of Campath-1H with a standard dose CHOP regimen, as the first-line treatment for PTCL patients

PATIENTS AND METHODS

Patients

To be enrolled in the trial patients had to meet the following criteria: (a) a histological diagnosis of PTCL unspecified (PTCL-U), or angioimmunoblastic-like T-cell lymphoma (AILD-T), or anaplastic large-cell T-cell lymphoma Alk-negative (ALCLAlk-); (b) confirmation of the histopathological diagnosis by the central review panel of expert pathologists of the University of Bologna or, alternatively, by a second expert pathologist of another referral center of pathology; (c) age greater than 16 and less than 70 years; (d) absence of major heart, liver, kidney or GI dysfunction except those related to lymphoma; (e) written informed consent; (g) absence of uncontrolled infection; (h) absence of other neoplasm or previous chemo-radiotherapy.

From June 2003 to December 2005 patients with a diagnosis of PTCL were consecutively enrolled in the trial by 14 Italian hematological institutions, on behalf of GITIL (Gruppo Italiano Terapie Innovative nei Linfomi). Overall, 25 patients were enrolled and assessed for feasibility and toxicity; however only 24 patients were evaluated for response, because one patient had a revised diagnosis of lymphoblastic lymphoma after pathological review (see below).

Pathological review

The pathologic material was available from 22 of the 25 enrolled patients and consisted of unstained sections (n=4) or paraffin blocks (n=18). The material was used for both diagnostic review and immunohistochemical localization of the CD52 molecule. In particular, the former was based on the evaluation of hematoxylin-eosin stained
preparations and a series of markers including: CD2, CD3, CD4, CD5, CD7, CD8, CD10, CD15, CD20, CD21, CD30, CD56, CD79a, PAX5/BSAP, and Mib-1. It should be noted that the markers could not be homogeneously assessed in all instances because for four of the cases only 10 unstained sections were available. The corresponding antibodies were used following appropriate antigen retrieval and detected using the alkaline phosphatase anti-alkaline phosphatase complexes (APAAP) technique. Anti-CD52 (rat anti-human, monoclonal; Serotec Ltd, Oxford, UK) was applied at a 1:200 dilution and visualized with the EnVision+ technique, as previously described. Prior to antibody exposure, the sections underwent antigen retrieval in citrate buffer (pH = 6.0) in a microwave at 900W (3 cycles lasting 5’ each). Two experienced pathologists (S.P. and C.C.) scored the CD52 results by estimating the number of positive cells. Cases were considered positive if 30% or more of the tumor cells were stained.

**Study design**

*Main protocol features.* The study protocol was a phase II, open-label trial performed among 14 Italian hematological Institutions. The study was approved by the ethics committee of the coordinating center and subsequently approved by the local ethic committee of the individual centers and by the national clinical trials agency. Written informed consent was obtained according to the Declaration of Helsinki.

The primary endpoints of the study were feasibility and toxicity of the treatment program; the secondary endpoint was the efficacy of the program, assessed in terms of achievement of complete remission (CR), one-year overall survival (OS) and one year failure-free survival (FFS).

To prevent excessive immunosuppression induced by Campath-1H when administered once a month for 8 months, the treatment program was split into two therapeutic schedules, differing only in the number of Campath-1H infusions, and stopping rules were
introduced. Phase I consisted of four courses of CHOP-C (CHOP supplemented with
Campath-1H), and four courses of standard CHOP. Phase II followed, consisting of eight
courses of CHOP-C. The first 4 patients enrolled were allocated to phase I; in the absence
of a serious adverse event (SAE: see below) in Phase I, the study shifted to phase II with
the second group of patients. Had a single SAE been reported during phase I, an
additional patient would have been enrolled in this phase. If another patient within this
group had developed a SAE, the trial would have been closed. The same protocol of
stopping rules was planned for phase II. SAE was defined as any adverse event directly
related to the therapy, occurring both during therapy or follow-up, including: (1) death, (2)
life-threatening complications, (3) disabling conditions, (4) a prolonged hospitalization
(more than three months).

**Treatment schedule.** The treatment schedule is summarized in figure 1. In the first cohort
of patients (patients 1-4: phase I) Campath-1H (Mabcampath® Schering AG – Berlin) was
given only at courses 1-4 and standard CHOP was administered for courses 5-8. In the
second cohort (patients 5-25: phase II) Campath-1H was administered at all CHOP
courses. Patients were given standard-dose CHOP chemotherapy for eight courses as
previously reported\(^25\). Cycles were repeated every 28 days. At the first course Campath-
1H was given subcutaneously with an escalated dose of 3mg, 10mg and 30 mg. on day -2,
-1 and 0, respectively, and the full 30-mg dose was given the day before for subsequent
courses. chlorphenamine 10 mg. i.v. was given one hour prior to Campath-1H
administration, along with paracetamole 500 mg. p.o. and alizapride 100 mg. i.v., were
administered 30 minutes prior to Campath-1H administration..

**Sample size.** A single-stage phase II study design was used to test the null hypothesis
that the true response rate was 40 - 45% against the alternative that it was 70%. A sample
size of 25 evaluable patients was planned, using A’Hern’s tables for exact single-stage
phase II designs\(^26\). If 15 or more responses were observed, the null hypothesis would be
rejected. With this scenario, the probability of one-sided type I error was 0.05 and the study power was 0.90.

**Anti-infective prophylaxis.** Prophylaxis against herpes simplex virus (HSV) and varicella-zooster herpes virus (HVZ), irrespective of a history of previous recurrent disease, was given to all patients with acyclovir tb. 400 mg. twice in a day. Prophylactic therapy against *Pneumocystis Carinii* with Sulphametoxazole-Trimethoprim tablets 800/160 mg twice in a day on alternate days was given or Pentamididine aerosol every 45 days in case of allergic reaction to cotrimoxazole. Ciprofloxacin 500 mg twice in a day was administered when neutrophil count decreased below 500/µl. The galactomannan assay for monitoring invasive aspergillosis was performed twice in a week in most patients, and itraconazole, oral solution, 400 mg/die twice a day, was administered during meals. Both galactomannan monitoring and antifungal prophylaxis were performed throughout the treatment and prolonged up to six months after the end of the chemotherapy. In case of two consecutive positive assays, antifungal therapy was started.

**Stopping rules** As mentioned above, the study was split into two phases based on for the total dose of Campath-1H administered and allowed for only one patient in phase I and one patient in phase II to present with a SAE. If any other patient beyond this threshold had developed a SAE, the study would have been closed. This protocol follows standard stopping rules as required for clinical trials conducted in good clinical practice.

**Disease evaluation**

Patients underwent a baseline staging with physical examination, involving a measurement of all the superficial pathological nodes, complete blood count (CBC), routine laboratory tests with liver and kidney function assessment, serologic testing for
anamnestic viral and fungal infection, total and differential count of CD3+, CD4+ and CD8+ lymphocyte counts, chest and abdominal computed tomography and/or PET scan and bilateral bone marrow trephine biopsy. The same hematological, biochemical and radiological tests were repeated at the end of the therapy and every 6 months thereafter during follow-up. Bone marrow trephine biopsy was repeated in the presence of bone marrow invasion at diagnosis. The response assessment was made according to the ECOG criteria of response to therapy for non-Hodgkin lymphoma\textsuperscript{27-28}.

**Statistical analysis**

All data were analyzed using the SAS program\textsuperscript{29}. OS and FFS curves were calculated according to the Kaplan-Meier method\textsuperscript{30}. OS was calculated from the date of diagnosis until death from any cause or date of last contact for living patients. For patients in CR, FFS was calculated from the date of diagnosis to the first evidence of failure. Failure was defined as (a) any treatment response different from CR or partial remission (PR), (b) disease relapse, (c) death for lymphoma or (d) death for treatment effects.

**RESULTS**

**Pathology review and CD 52 expression**

The diagnosis of peripheral T-cell lymphoma (PTCL) was confirmed by the central review panel in 19 of 22 cases, and defined according to the World Health Organization (WHO) Classification (8 PTCL-U, 7 AILD-T, 3 ALCL Alk-, and 1 enteropathy-associated)\textsuperscript{3}. The biopitic sample was insufficient in two cases, while the original diagnosis was not confirmed for one patient, who was diagnosed as T-lymphoblastic lymphoma (TdT-positive) at the pathological review. In three cases (2 PTCL-U and 1 ALCL ALK-negative) the diagnosis was confirmed by the local referral pathologists. CD52 was analyzed in 19 of 24 patients.
In 5 patients CD 52 assay could not be done either for absence (3 cases) or insufficient material (2 cases). CD 52 was evaluable in 15 of 19 cases, 11 that were CD52-positive and four that were negative. In the remaining four cases (2 with unstained sections and 2 with paraffin blocks available), antigen preservation was on the whole poor as shown by the immunohistochemical results for most antibodies employed.

Clinical characteristics of the patients

The clinical characteristics of the 24 patients evaluable for both toxicity and response to CHOP-C are reported in Table 1. The mean age was 52.0 years (28-69) and all but three showed advanced disease (stage III-IV). Bulky disease was recorded in 2, bone marrow involvement in 10, high LDH values in 12 and an IPI 0 in 1 patient, 1 in 7 patients, 2 in 7 patients, 3 in 7 patients, 4 in 2 patients.

Treatment feasibility and dose intensity

Overall, 25 patients entered the study protocol and were valuable for treatment feasibility and toxicity. Patients 1 through 4 were treated with CHOP-C for four cycles, followed by four courses of standard CHOP, patients 5-21 received the planned 8 CHOP-C courses, while only 6 CHOP-C courses were delivered to patients 22 through 25, as a result of individual physician decision.

The relative dose intensity (RDI) was calculated according to Hryniuk and Bush. The mean dose intensity was 210 mg/m²/wk (RDI=96%) for cyclophosphamide, 14 mg/m²/wk (RDI=90%) for doxorubicin, 0.29 mg/m²/wk (RDI=94%) for vincristine, 85 mg/m²/wk (RDI=59%) for prednisone and 8.0 mg/m²/wk for Campath-1H (RDI=88%). In one patient, aged 69, vincristine was administered at half-dose for all CHOP-C courses (1 mg every cycle). The RDI was slightly lower for Campath-1H and prednisone because in two
patients who developed invasive aspergillosis due to severe immunodepression, both drugs were reduced.

**Treatment response**

Response is summarized in Table 2. Among 24 evaluable patients, 17 (71%), reached CR, 1 had PR, with an overall response rate (CR+PR) of 75%; the remaining patients had either stable or progressive disease. All the patients affected by AILD-T (6/6), ALCL (3/3) and EATCL (1/1) entered CR while only 50% of PTCL-u patients (7/14) showed a CR. CD52 expression could be evaluated in 15 patients: 4 were found negative and 11 positive. Two of the four patients with a CD 52-negative phenotype progressed during therapy and two entered CR, while 8 (73%) patients with the CD 52-positive phenotype reached CR.

As shown in Table 2, after a mean follow-up of 495 days (217-1186), 14 of 24 patients were still alive, and 10 had died. Of the 24 patients 17 achieved CR, 1 PR and 1 minimal response (MR). Five patients showed progression early during therapy: 1 after two courses, 1 after three courses and 3 after four courses. Fourteen patients are presently alive. So far, nine patients have died as a result of resistant lymphoma, including the 7 patients not in CR at the end of treatment and 2 patients in relapse; one more patient died from pneumonia while in CR, 6 months after treatment completion; this complication could be a consequence of the immunosuppressive treatment and therefore considered as a treatment failure. Thirteen patients are presently in continuous CR, while four patients (3 in CR and 1 in PR) experienced disease relapse at 3, 4, 5 and 8 months after treatment completion.

As shown in Figure 2A the OS curve is projected to 70% and 53% at one and two yr, respectively. As shown in Figure 2B the FFS curve is projected to 54% and 48% at one and two yr, respectively.
**Adverse events**

Toxicity was evaluated for all 25 patients who were treated with CHOP-C for a total of 176 courses.

**Infusion-related.** Infusion-related adverse events were recorded after Campath-1H administration in 7 patients: a mild febrile spike (up to 38 °C) was transiently observed in 4 patients at different CHOP-C administrations, and 3 more patients occasionally displayed a local erythema around the injection site during the first three courses. No grade 4 reactions were observed.

**Hematologic toxicity.** Neutropenia was by far the most frequent manifestation of hematological toxicity, with severe neutropenia recorded in 59 of 176 cycles (34%). Thrombocytopenia was less frequent, and severe thrombocytopenia was observed in only 4 of 176 (2%) cycles. Anemia was even less frequent, and a reduction of more than 2 g/dl compared to the baseline values was recorded in 6 of 24 patients (25%) at the end of treatment. The most severe hematological toxicities were usually observed following the first CHOP-C course. Combined Campath-1H and CHOP administration produced a profound decline in circulating T-lymphocytes: mean CD3, CD4 and CD8 values before treatment were 1042, 529 and 394 cells/µl respectively, while these values dropped to 239, 156 and 305 cells/µl respectively, after treatment. The values steadily increased thereafter and reached normal levels within 6 months in all but two cases.

**Non-hematologic toxicity.** Infectious complications were by far the most frequent non-hematological toxicities (see Table 3). CMV reactivation, without evidence of pneumonia, was diagnosed by immunofluorescent detection of p65-bearing leukocytes and/or viral DNA detection by PCR analysis in at least two consecutive samples. With these diagnostic tools, CMV reactivation was detected in 15 of 176 courses (9%). All patients diagnosed with CMV reactivation received pre-emptive foscarnet or gancyclovir, usually
with a rapid return to normal serological results and disappearance of any symptoms possibly related to CMV reactivation. In one patient, left facial nerve palsy and hyposthenia in a left lower limb appeared one month after the completion of the chemotherapy: a cranial NMR showed a picture evocative of JC virus encephalitis, and the diagnosis was confirmed in CSF fluid by PCR. The patient is now in continuous CR but with a clinical picture of irreversible dementia: this complication is related to the severe immunosuppression induced by the treatment and therefore should be considered a treatment failure. Two patients developed invasive aspergillosis. The first patient developed a lung infiltrate after the third CHOP-C course and was treated with voriconazole for four months with complete clearance of the lesion. This patient received a fourth CHOP course without Campath-1H with approximately a one-month delay, then received the remaining four courses regularly, all supplemented with Campath-1H. The second patient developed pulmonary invasive aspergillosis after the fourth CHOP-C course, and underwent systemic antifungal therapy for a month, with a favorable outcome; this patient also resumed the therapy with a one-month delay. One patient developed PC pneumonia, treated successfully with co-trimoxazole. Bacterial infectious complications included: one patient with *Staphylococcus Aureus* sepsis related to the surgical biopsy and one with *Streptococcal* sepsis, and both responded to wide-spectrum antibiotics. There also was one patient with bacterial pneumonia sensitive to wide-spectrum antibiotics, occurring after the fifth cycle. Enlarged abdominal nodes were observed in one patient after the eight CHOP-C courses: ultrasound fine needle biopsy showed granulomatous adenopathy with Ziehl-Nielsen- positive elements, probably related to atypical mycobacteriosi; however, re-evaluation three months later showed the almost complete disappearance of the abdominal nodes without any specific treatment. Finally one patient developed fever of unknown origin (FUO) after the eighth CHOP-C course,
that was resistant to empiric antibiotic therapy; the fever subsided upon resolution of neutropenia without any microbiological evidence of a specific etiologic agent.

**Other mild side effects.** Three patients showed signs of neurotoxicity: two presented a grade 2 obstinate constipation probably related to itraconazole, and one a grade 2 peripheral neuropathy.

**DISCUSSION**

The present study reports the results of a prospective, multicenter trial to evaluate the feasibility, safety and efficacy of the combination of Campath-1H (alemtuzumab) and CHOP (CHOP-C) as first-line treatment for patients with PTCL. Campath-1H was employed at the low dosage of 30 mg per CHOP course which helped make the program feasible. Indeed, CHOP-C was deliverable to all patients, with minor dose reductions in a few cases. Nevertheless, infectious complications were not only frequent but also severe and life-threatening in a few patients. On the other hand, Campath-1H given at 30 mg along with CHOP-C produced a high rate of stable CR. This result is quite encouraging and suggests that chemo-immunotherapy may represent a major advance in the management of PTCL, provided that careful monitoring and prompt treatment of infectious complications are implemented in those new schedules that include Campath-1H.

The term PTCL designates an heterogeneous group of T-cell malignancies characterized by an aggressive behavior and a dismal prognosis, with less than 30% of patients being cured by anthracycline containing therapies, such as CHOP or CHOP-like regimens. Because of these disappointing results, other strategies have been explored, including high-dose chemotherapy and autografting. So far, most of the published studies, with ASCT both as salvage or first-line therapy have failed to show any significant advantage over standard treatment with standard chemotherapy (CHOP or CHOP-like regimens). Two recent publication have prospectively explored the
role of ASCT as a first-line treatment after high-dose chemotherapy in an intent-to-treat and long-term analysis, and both failed to show any advantage over standard treatment\textsuperscript{20, 33}. Chemo-immunotherapy combining anti-lymphoma cell monoclonal antibody and chemotherapy is presently the most innovative and effective approach in the management of lymphoma, specifically B-cell subtypes\textsuperscript{34-36}. The CD52 antigen seems a suitable target for chemo-immunotherapy programs for PTCL, given the availability of the anti-CD52 alemtuzumab (Campath-1H). The glycosylphosphatidylinositol-anchored membrane glycoprotein CD52 is detectable by cytofluorimetric assay on normal and pathologic B- and T-cell populations, with the highest values observed in some T-cell neoplasm such as T-PLL, although the expression of this molecule has been found detectable in less than 50% of PTCL samples evaluated using a standard immunohistochemical procedure\textsuperscript{21-22}.

The inclusion of Campath-1H in therapeutic programs for T-cell disorders has been considered with increasing interest in the last few years. Preliminary observations have shown some promising results in different T-cell malignancies, including T-PLL, cutaneous T-cell lymphomas, and T-cell large granular lymphocytic leukemia\textsuperscript{37-40}. So far, a single study has been performed with alemtuzumab in PTCL in a series of 14 PTCL patients failing one or two lines of chemotherapy. Campath-1H was given alone at 30 mg subcutaneously three times a week for a maximum of 12 weeks and produced an overall response rate of 36%, with 3 patients achieving CR and 2 PR. Despite these encouraging results, the study was closed because of unacceptably high toxicity, with 5 treatment-related deaths\textsuperscript{41}. Quite recently a very preliminary report has been published on 20 patients treated with CHOP-C with the same schedule of the present study, with courses repeated every 21 days. The CR rate was 65% and the estimated event-free survival at 1 year was 43\%\textsuperscript{42}. These results, albeit similar to ours, are the report of an interim analysis of an ongoing trial and are too preliminary for a comment.
These considerations taken together prompted us to design a prospective trial to evaluate alemtuzumab in combination with chemotherapy in PTCL. In planning the trial, we carefully considered the following main issues: (a) the very aggressive behavior of PTCL; (b) the potential risks of infectious complications with Campath-1H; (c) the need of combining Campath-1H with a chemotherapy program well defined for both toxicity and clinical efficacy, and (d) the unequivocal histopathological diagnosis of PTCL of patients entering the study protocol. Thus, a study protocol was designed for patients with PTCL at disease onset; the program included the use of a standard CHOP regimen supplemented with alemtuzumab. To prevent excessive immunosuppression the dose of Campath-1H was 30 mg in each course, which represents a much lower dosage compared to that employed in previous studies; the cycles were administered every four weeks instead of three weeks. An histopathologic review of the diagnostic sample was performed in all cases.

Combining Campath-1H with standard CHOP chemotherapy proved to be quite effective in terms of treatment response: 18 patients responded with an overall response rate of 75%: 17 patients entered CR and 1 PR. Of the 17 patients in CR, the response was durable in 14 patients with a median CR duration 11 months. This result compares favorably with the less than 50% CR rate reported with CHOP or CHOP-like regimens\textsuperscript{2,3,8,13}. At this writing, only three of the 17 patients in CR and 1 patient in PR have relapsed.

The results are even more relevant if one considers that all but three patients showed at presentation an advanced stage, with a high LDH value in half of them (50%), bone marrow involvement in 41% and an age over 60 years on one third of patients. All these parameters have been shown to have adverse prognostic significance in the prognostic model for peripheral T-cell lymphoma unspecified (PIT)\textsuperscript{4}. Indeed, the median CR duration of 11 month looks quite promising if one considers that almost half of the patients with PTCL die because of their disease within one year following conventional treatments\textsuperscript{4}.  
Although the numbers in this study were very small, the patients treated with 8 CHOP-C courses seemed to respond better than the ones treated with 4 CHOP-C: 33% versus 76%, respectively. This outcome could suggest that the second schedule is the efficacious one and could prompt us to plan a future treatment schedule with CHOP-C 21 or even CHOP-C 14 instead of CHOP-C 28.

The histopathologic diagnosis was carefully reviewed in all patients, with additional immunohistochemical studies in most diagnostic samples. In addition, expression of CD52 was assessed whenever possible. In our series, 11 of 15 evaluable patients had neoplastic cells positive for CD52, with an higher percentage than those found by Rodig et al.22 and Piccaluga et al.43. It has been reported that CD52 expression might correlate with treatment outcome in T-PLL21. However, we could not show any relationship between CD52 expression and treatment outcome in our series, but this might reflect the limited number of patients enrolled. The same holds true for the CD52 positivity prevalence among PTCL patients recorded in the present study: for instance, Piccaluga et al. – who obtained much lower figures – evaluated 93 cases43. Thus, prospective studies on larger collectives are warranted to understand predictive value of CD52 determination. Our results might indicate that the intensity rather than the percentage of CD52 expression by neoplastic cells is relevant and may predict tumor response to alemtuzumab. This hypothesis is supported by recent in vitro observations in experimental models44. Alternatively, one can speculate that Alemtuzumab might eliminate surrounding normal CD52 positive cells, leading to damage to the microenvironment and, as a consequence, to a weakened survival of neoplastic cells. Whatever the mechanisms, the combination of Campath-1H and CHOP represents an innovative and really effective treatment for a disease poorly responsive to currently available therapies.

Despite a thorough program of anti-infective prophylaxis and watchful clinical monitoring, the main problem we faced in our study was the high incidence and severity of infectious
complications. Indeed, life-threatening infections occurred in one quarter of the patients (2 invasive aspergillosis, 1 J-C viral encephalitis, 1 sepsis, 1 pneumonia, and 1 suspected tuberculosis). The total and differential counts of T cell were not checked cycle by cycle in all the patients: in three patients the CD3 values dropped below 500 cells/µl after the third course of chemotherapy: for these reason is likewise that the severe T depletion was the main cause for these serious infections. These numbers confirm that Campath-1H therapy is associated with marked immunosuppression and consequently with an increased risk of infections by various agents, as already observed in previous experiences with alemtuzumab in patients with T-cell disorders\textsuperscript{38-39, 41}. Moreover, in a few patients transient severe neutropenia or even pancytopenia were observed; however incidence, degree and duration were similar to those reported in previous studies with Campath-1H in PTCL\textsuperscript{38,39,41}. In fact, the main toxicity associated with alemtuzumab is probably the suppression of T-cell function and the absolute drop in the number of CD4 cells. These factors are responsible for the opportunistic infections that remain the most serious problem during and after Campath-1H administration. Attempts to minimize the risk of infectious complication, using new strategies such as pre-emptive therapies based on a very early diagnosis of viral or fungal infection and/or the infusion of CTL raised against specific viral or fungal targets should be possibly considered and included in Campath-1H-containing programs\textsuperscript{45-46}. A number of new drugs less immunosuppressive are at present under evaluation in PTCL: among these Gencytabine alone\textsuperscript{47} or in combination\textsuperscript{48}, the histone deacetylase inhibitors Depsipeptide\textsuperscript{49} and SAHA\textsuperscript{50}, the purine analog Nelarabine\textsuperscript{51} and new antifolate drugs such as Pralatrexate. All these drugs showed a mild to moderate activity in PTCL, with the noteworthy exception of Pralatrexate: the latter, in a phase 2 pilot study, was able to induce CR in 4 out of 5 heavily pretreated PTCL. Three of the 4 responding patients remained in CR 4-9 months, with no other side effects than a mild stomatitis\textsuperscript{52}. 
In conclusion, the results of our prospective trial demonstrate that CHOP-C is a practicable and effective regimen for PTCL patients at diagnosis, inducing a high rate of CR; its efficacy, however could be potentially hampered by the non-negligible percentage of infectious complications reported in this study: at this writing a number of phase III randomized trials comparing CHOP-C followed by autologous stem cell transplantation to traditional CHOP or CHOP-like regimens followed by the same intensive regimen are underway. Only these randomized trials could clarify the confines of the risk/benefit ratio of this combination regimen. Recently encouraging results in terms of OS and PFS have been reported using reduced-intensity conditioning (RIC) allogeneic transplantation in patients with relapsed or primary refractory PTCLs\textsuperscript{53}. Based on these findings, it has been suggested that patients with an HLA-identical donor and poor prognostic features at diagnosis might be included in investigative trials of RIC, followed by allografting. However, an adequate tumor reduction if not a complete remission is a prerequisite for a successful allogeneic procedure. Thus, CHOP-C can be considered a suitable up-front treatment for PTCLs that ensures a high response rate; responsive patients with an adverse prognostic presentation and an HLA-identical donor may subsequently be considered for RIC allograft. This combined approach is now under evaluation in an ongoing multicenter study at our institutions in Italy.

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AUTHOR CONTRIBUTION STATEMENT

Andrea Gallamini: designed research and wrote the paper
Corrado Tarella: designed research and reviewed the paper
Francesco Zaja: reviewed the paper
Pierfederico Torchio: analyzed the data
Stefano Pileri: Reviewed the histopathology and reviewed the paper
All the authors but S Pileri and P Torchio collected clinical data
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Table 1. Main patient characteristics

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<th>Parameter</th>
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<td>Histological subtype(^2)</td>
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<td>• PTCL-U</td>
<td>14 (58.3)</td>
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<td>• AILD-T</td>
<td>6 (25.0)</td>
</tr>
<tr>
<td>• ALC-Alk-</td>
<td>3 (12.5)</td>
</tr>
<tr>
<td>• EATCL</td>
<td>1 ( 4.2)</td>
</tr>
<tr>
<td>Ann Arbor Stage</td>
<td></td>
</tr>
<tr>
<td>• III-IV</td>
<td>21 (87.5)</td>
</tr>
<tr>
<td>B symptoms</td>
<td>11 (45.8)</td>
</tr>
<tr>
<td>BM involvement</td>
<td>10 (41.7)</td>
</tr>
<tr>
<td>Elevated LDH serum level</td>
<td>12 (50.0)</td>
</tr>
<tr>
<td>IPI score</td>
<td></td>
</tr>
<tr>
<td>• 0 - 1</td>
<td>8 (33.3)</td>
</tr>
<tr>
<td>• 2 - 3</td>
<td>14 (58.3)</td>
</tr>
<tr>
<td>• 4 - 5</td>
<td>2 ( 8.3)</td>
</tr>
</tbody>
</table>

\(^1\) 25 patients entered the study program and are evaluable for treatment feasibility and toxicity; however, one patient had a revised diagnosis of lymphoblastic lymphoma and is excluded from the response analysis
\(^2\) PTCL-U: Peripheral T Cell Lymphoma-Unspecified; AILD-T: angio-immunoblastic T-cell lymphoma; ALC Alk-: Anaplastic Large Cell lymphoma ALK negative; EATCL: enteropathy-associated T-Cell Lymphoma

Table 2. Response to treatment of 24 evaluable PTCL patients

<table>
<thead>
<tr>
<th>Response parameter(^1)</th>
<th>Histopathology</th>
<th>n =   (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>PTCL-U (7/14) AILD-T (6/6) ALC-L (3/3) EATCL (1/1)</td>
<td>17 (70.8)</td>
</tr>
<tr>
<td>PR</td>
<td>PTCL-U (1/14)</td>
<td>1 (4.2)</td>
</tr>
<tr>
<td>Minor Response</td>
<td>PTCL-U (1/14)</td>
<td>1 (4.2)</td>
</tr>
<tr>
<td>Disease progression</td>
<td>PTCL-U (5/14)</td>
<td>5 (20.8)</td>
</tr>
<tr>
<td>Patients alive</td>
<td>PTCL-U (5/14) AILD-T (6/6) ALC-L (3/3)</td>
<td>14 (58.3)</td>
</tr>
<tr>
<td>• median follow-up, mos. (range)</td>
<td>16 (5 – 42)</td>
<td></td>
</tr>
<tr>
<td>Patients alive in CCR</td>
<td>PTCL-U (5/14) AILD-T (5/6) ALC-L (3/3)</td>
<td>13 (54.2)</td>
</tr>
<tr>
<td>• median follow-up, mos. (range)</td>
<td>11 (5 – 42)</td>
<td></td>
</tr>
</tbody>
</table>

\(^1\) CR : Complete Remission ; PR : Partial Remission
Table 3. Major (WHO 4) infections

<table>
<thead>
<tr>
<th>Patient n°</th>
<th>CIC</th>
<th>Age</th>
<th>Histol.</th>
<th>Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>UD1</td>
<td>57</td>
<td>PTCL-U</td>
<td>Invasive Aspergilosis, J-C Viral Encephalitis</td>
</tr>
<tr>
<td>4</td>
<td>GE1</td>
<td>64</td>
<td>ALK-</td>
<td>Staphilococcus sepsis, Streprococcus sepsis</td>
</tr>
<tr>
<td>7</td>
<td>SP1</td>
<td>65</td>
<td>PTCL-U</td>
<td>Bacterial Pneumonia, PC pneumonia</td>
</tr>
<tr>
<td>15</td>
<td>TO1</td>
<td>69</td>
<td>PTCL-U</td>
<td>Bacterial Pneumonia, Invasive Aspergilosis</td>
</tr>
</tbody>
</table>
Figure 1: Two-phases schedule of CHOP-C administration
Figure 2: Kaplan-Meier’s estimates of the overall survival (A) and failure free survival (B) distribution function of all 24 patients.
Alemtuzumab (Campath-1H) and CHOP chemotherapy as first-line treatment of peripheral T-cell lymphoma: results of a GITIL prospective multicenter trial

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