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Intensified chemo-immunotherapy with or without stem cell transplantation in newly diagnosed patients with peripheral T-cell lymphoma

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Abstract

Peripheral T-cell lymphomas (PTCLs) receiving conventional treatment have a poor clinical outcome. We conducted a phase II study to evaluate the feasibility and efficacy of chemo-immunotherapy in young (<60 years old, Clin A study) and elderly (>60 and <75 years old, Clin B study) patients with newly diagnosed PTCL. Clin A patients ($n=61$) received two courses of CHOP (cyclophosphamide, adriamycin, vincristine, prednisone)-21 with alemtuzumab (AL, 30 mg) followed by two courses of high-dose chemotherapy. On the basis of donor availability, patients in response received allogeneic (allo) or autologous (auto) stem cell transplantation (SCT). Clin B patients ($n=25$) received six courses of CHOP-21 and AL (10 mg). Clin A responding patients were 38 of 61 (62%) and received alloSCT ($n=23$) or autoSCT ($n=14$); one complete remission (CR) patient was not transplanted. At a median follow-up of 40 months, the 4-year overall survival (OS), progression-free survival (PFS) and disease-free survival (DFS) rates were 49, 44 and 65%, respectively. In Clin B study, the response rate was 72%. At a median follow-up of 48 months, the 4-year OS, PFS and DFS rates were 31, 26 and 44%, respectively. In conclusion, front-line alloSCT or autoSCT is effective in prolonging DFS in young patients; AL in elderly improved response with no survival benefit.

Introduction

Peripheral T-cell lymphomas (PTCLs) are a rare and heterogeneous group of lymphoid malignancies usually presenting with advanced stage disease. CHOP (cyclophosphamide, adriamycin, vincristine, prednisone) or CHOP-like regimens are still considered as the standard treatment for PTCLs¹ and are associated with a dismal outcome of a 5-year overall survival (OS) in ~25–30%. Anaplastic large cell lymphoma (ALCL), expressing the anaplastic lymphoma kinase (ALK), represents an exception with a more favorable outcome.²

In recent years, different trials have focused on modifications of conventional chemotherapy. The German High-Grade Non-Hodgkin Lymphoma study group showed that the addition of etoposide to CHOP (CHOEP) improved event-free survival (EFS) in a selected cohort of young patients with normal lactate dehydrogenase values, essentially including ALK-positive ALCL (3-year EFS of 91%),³ but failed to improve the outcome of elderly patients. Due to a consistent expression of CD52 antigen in PTCL-not otherwise specified (PTCL-NOS) and angioimmunoblastic lymphomas (AILT),^{4, 5} the anti-CD52 monoclonal antibody (alemtuzumab, AL) was used to explore the role of chemo-immunotherapy in PTCLs. Phase II trials combining CHOP and AL reported promising response rates. However, the 2-year EFS was not improved, suggesting that a consolidation was probably required.^{6, 7, 8}

Therapy intensification with up-front autologous stem cell transplantation (autoSCT) was explored in phase II studies and resulted in a 3-year EFS ranging from 30 to 50%.^{9, 10, 11, 12} Recently, the Nordic Lymphoma group reported the results of up-front autoSCT following six courses of CHOEP-14. With a median follow-up of 60 months, the estimated 5-year OS and progression-free survival (PFS) were 51 and 44%, respectively.¹³ With regard to salvage therapy, allogeneic SCT (alloSCT) has been used in small cohorts of patients with a 3-year OS ranging from 40 to 60%.^{14, 15,}

Bearing in mind all these findings, we designed a phase II trial enrolling young (< 60 years old, Clin A study) and elderly (>60 and < 75 years old, Clin B study) patients. Patients in Clin A study received an induction phase consisting of CHOP-AL and high-dose chemotherapy followed by consolidation with alloSCT or autoSCT, depending on donor availability. Patients in Clin B study received a reduced dose of AL in combination with CHOP to increase the response rate while limiting toxicity.

Materials and methods

Patient characteristics

From November 2006 to November 2010, 92 patients were enrolled by 18 Italian Centers. Eligibility criteria were the following: (1) histologically proven diagnosis of PTCL-NOS, ALK-negative ALCL, AILT or enteropathy-associated T-cell lymphoma (EATL); (2) advanced stage disease (stage II–IV) or stage I disease with an International Prognostic Index (IPI) score of < 2; (3) preserved organ function; (4) the absence of prior chemo-radiotherapy. Diagnosis was performed according to the WHO (World Health Organization) classification and verified by a central pathology review.^{17, 18} In our trial, the expression of CD52 was not assessed on paraffin blocks.

Patient characteristics are reported in Table 1. Clin A enrolled 64 patients, although 3 were excluded: 2 after pathological review (T-lymphoblastic lymphoma ($n=1$); ALK-positive ALCL ($n=1$)) and 1 for previous radiotherapy. In all, 61 patients were analyzed: 33 PTCL-NOS, 12 ALK-negative ALCL, 14 AILT and 2 EATL. The median age was 48 years old (range: 24–60 years old). Clin B enrolled 28 patients before it was stopped for toxicity by the Data and Safety Monitoring Board. Three patients were excluded from the analysis: two patients died before starting the treatment protocol (myocardial ischemia ($n=1$), progressive disease ($n=1$)) and one who was diagnosed as T-lymphoblastic lymphoma. Analysis was performed on 25 cases: 9 PTCL-NOS, 7 ALK-negative ALCL, 7 AILT and 2 EATL.

Table 1 - Patient characteristics at diagnosis.

Table 1. Patient characteristics at diagnosis				
Characteristic	Clin A (n = 61)		Clin B (n = 25)	
Median age, years (range)	48 (24–61)		68 (60–75)	
Male/Female	35/26	57%/43%	15/10	60%/40%
<i>Histology</i>				
PTCL-NOS	33	54%	9	36%
ALK-negative ALCL	12	20%	7	28%
AITL	14	23%	7	28%
EATL	2	3%	2	8%
<i>Ann Arbor stage</i>				
Stage I–II	5	8%	0	0
Stage III–IV	56	92%	25	100%
<i>IPI score</i>				
<2	19	31%	0	0
≥2	42	69%	25	100%
<i>PIT group</i>				
1–2	42	69%	3	12%
3–4	19	31%	22	88%
<i>Extranodal disease</i>				
Liver ± Gastrointestinal	14	23%	7	28%
Others	47	77%	18	72%

Abbreviations: AILT, angioimmunoblastic lymphoma; ALK-negative ALCL, anaplastic lymphoma kinase-negative anaplastic large cell lymphomas; EATL, enteropathy-associated T-cell lymphoma; IPI, international prognostic index; PIT, prognostic index for PTCL-NOS; PTCL-NOS, peripheral T-cell Non-Hodgkin lymphomas–not otherwise specified.

The study was approved by the Ethical Committees of participating centers and received a grant for Good Clinical Practice conduction from the Italian Ministry of Health. Written informed consent was obtained from all patients. The study was registered in the University Hospital Medical Information Network Clinical Trials Registry (EudraCT Number 2006-004234-33).

Treatment plan

Clin A consisted of an induction and a transplantation phase (Figure 1). *Induction phase*: consisted of (1) CHOP (doxorubicin 50 mg/m², vincristine 1.4 mg/m² (maximum total dose 2.0 mg), cyclophosphamide 750 mg/m² intravenously on day 1, prednisone 100 mg orally on days 1 through 5) and intravenous AL (Mabcampath, Genzyme Europe, Netherlands) administered according to the following schedule: 3 mg, 10 mg, 20 mg, days –2, –1, 0 (before the first CHOP cycle), 30 mg on day 0 from the second CHOP cycle; (2) two courses of HyperCHidam: high-dose methotrexate given as a continuous infusion (1.6 g/m²) on day 1; cyclophosphamide 300 mg/m² and high-dose cytarabine 2 g/m² every 12 h for 3 days. Granulocyte-colony stimulating factor 5 mcg/kg per day was given from day +5.¹⁹ Leukaphereses were planned after the first or second (in case of marrow involvement) HyperCHidam. *Transplantation phase*: Patients achieving a partial (PR) or complete remission (CR) with an human leukocyte antigen-identical sibling (or 1 antigen mismatched) or with a matched unrelated donor received alloSCT. The conditioning regimen included thiotepa, fludarabine and cyclophosphamide, as previously described.²⁰ Anti-thymocyte globulin was

administered for mismatched siblings and unrelated donors (thymoglobulin 3.5 mg/kg daily on days -4 and -3). This regimen was followed by the infusion of alloSCT ($5-8 \times 10^6$ /kg CD34+) (on day 0). The donors included 13 matched siblings and 10 matched unrelated donors.

Figure 1. Flow chart of the Clin A and Clin B studies.

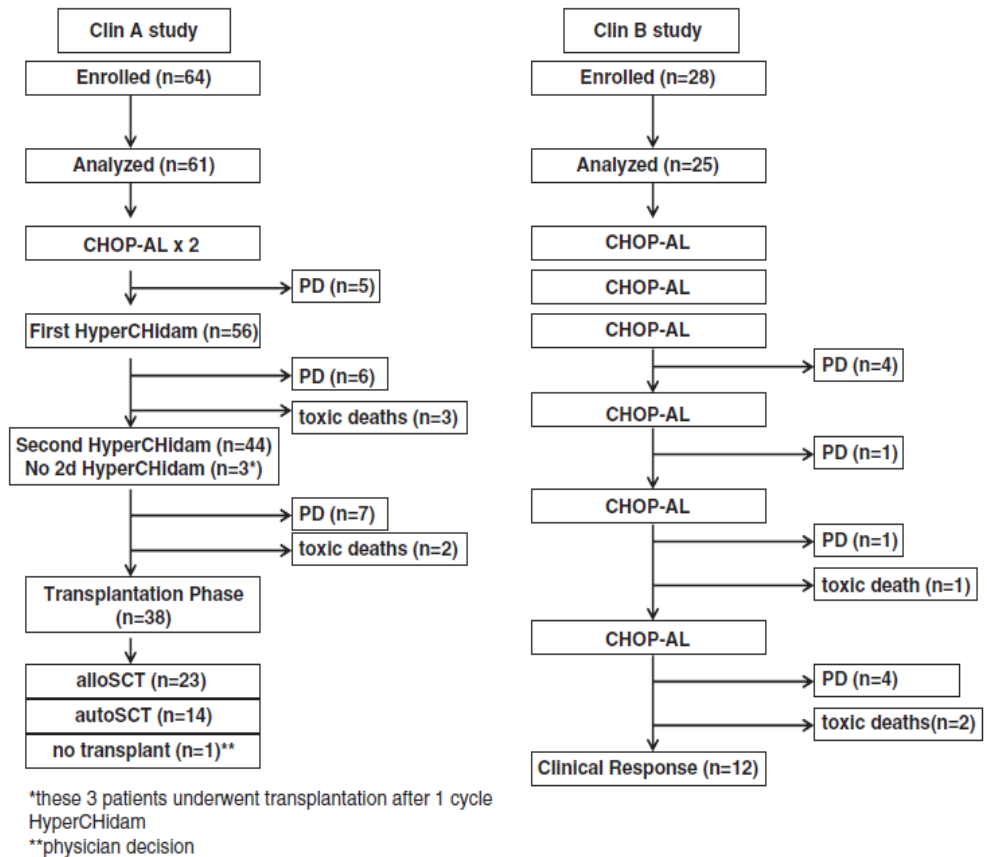


Figure 1. Flow chart of the Clin A and Clin B studies.

For patients in clinical response without a suitable donor, autoSCT was performed following a regimen consisting of carmustine, etoposide, cytarabine and melphalan (BEAM). The infusion of autologous peripheral blood progenitor cells was performed on day 0 ($>4 \times 10^6$ CD34+/kg).

Clin B consisted of a combination of AL (10 mg) and CHOP for six courses (CHOP-21) (Figure 1). Additional information is provided in the Supplementary Information.

Response assessment and toxicity criteria

The response to therapy was defined according to Cheson *et al.*²¹ In Clin A, treatment response was evaluated after the induction phase, 1 month after transplant and then every 3 months for the first 2 years and every 6 months thereafter. In Clin B, response was evaluated after 3 and 6 cycles, every 3 months for the first 2 years and every 6 months thereafter. Toxicity assessment was performed according to NCI Criteria for adverse events, version 3.0, cancer therapy evaluation program, CTCAE (<http://ctep.cancer.gov>).

Study design and statistical methods

The study included two prospective phase II trials: Clin A designed for young patients (18 and

60 years old) and Clin B for the elderly (>60 and 75 years old). Both Clin A and Clin B studies were planned according to the Simon optimal two-stage study design.²² Efficacy analyses were performed on all accrued patients, by the intention-to-treat principle. The primary end point was treatment efficacy defined as CR maintained for at least 6 months. Secondary end points were disease-free survival (DFS, estimated on two subsets: (1) all CR patients; (2) only CRs maintained for at least 6 months), PFS, OS, non-relapse mortality (NRM) incidence and relapse incidence. The Kaplan–Meier method was used to estimate the DFS, PFS and OS curves, which were compared using the log-rank test. The crude cumulative incidence curves of NRM were estimated considering relapse as a competing event, and comparisons between curves were carried out using the Gray test.²³ Univariate analyses (Kaplan–Meier and crude cumulative incidence curves) were performed

according to the patient's age (<48 years (median value), 48 years), sex, IPI, prognostic index for PTCL-NOS (PIT), histological subtype, the presence or absence of extranodal disease (liver/gastrointestinal involvement) and transplant type (auto, allo). Multivariable analyses of PFS and OS were performed using Cox regression models,²⁴ which included clinical response modeled as a binary time-dependent variable, together with patient's age (as continuous variable), IPI and extranodal disease as adjustment factors. In Clin A only, alternative models included transplantation as a binary time-dependent variable instead of clinical response. Additional information is provided in the Supplementary Information.

Results

Response to treatment: Clin A study

CHOP-AL therapy was started in 61 patients, but 5 progressed after the first ($n=3$) or the second cycle ($n=2$) and received a salvage therapy; 56 patients received the first HyperCHidam course, whereas the second was administered to 44 patients. The median time between cycles of CHOP-AL was 23 days (range, 19–60). The median time between cycles of HyperCHidam was 39 days (range, 19–87).

The reasons for not receiving the second HyperCHidam cycle were the following: PD ($n=6$), toxic deaths ($n=3$), grade 3–4 adverse events during the first cycle ($n=3$). These last three patients proceeded directly to the transplantation phase. Overall, at the end of the induction phase, 40 of 61 patients responded (65%), and among them there were 33 CRs (54%) and 7 PRs (11%). In all, 37 of 40 patients underwent alloSCT ($n=23$) or autoSCT ($n=14$); 2 patients in the CR group died of infectious complications before transplantation, and 1 CR patient did not receive autoSCT due to a prior systemic herpes-zoster infection complicated by prolonged neutropenia. Thus, 24 of 61 patients (39%) enrolled in this intensified program did not undergo transplantation because of three reasons: (1) progressive disease ($n=18$); (2) toxic death ($n=5$); (3) physician decision ($n=1$ in CR).

Before alloSCT, 20 patients (87%) were in CR and 3 (13%) in PR. At a median follow-up of 44 months, 16 patients were still in CR, whereas 4 have relapsed (17%) and died of PD. The last three patients, who were in CR before alloSCT, died of NRM after allograft (pneumonia ($n=1$), encephalitis ($n=1$) and acute graft-vs-host disease (GVHD) ($n=1$)).

Twenty-three patients received alloSCT ($n=13$ from matched sibling donors and $n=10$ from matched unrelated donors). Only 22 patients were evaluable for acute GVHD (1 patient died early for NRM). Acute GVHD of grade 2–4 occurred in 9 of 22 patients (40%) (only 2 experienced GVHD of grade III and IV). Only 22 patients were evaluable for chronic GVHD (2 were not evaluable for early death); chronic GVHD occurred in 11 of 21 patients (52%) ($n=9$ limited and $n=2$ extensive).

Before autoSCT, 10 patients (71%) were in CR and 4 in PR (29%). At a median follow-up of 32 months, all but 1 patient were alive in CR. Four patients relapsed, and three of them achieved long-term remission with salvage alloSCT.

Response to treatment: Clin B study

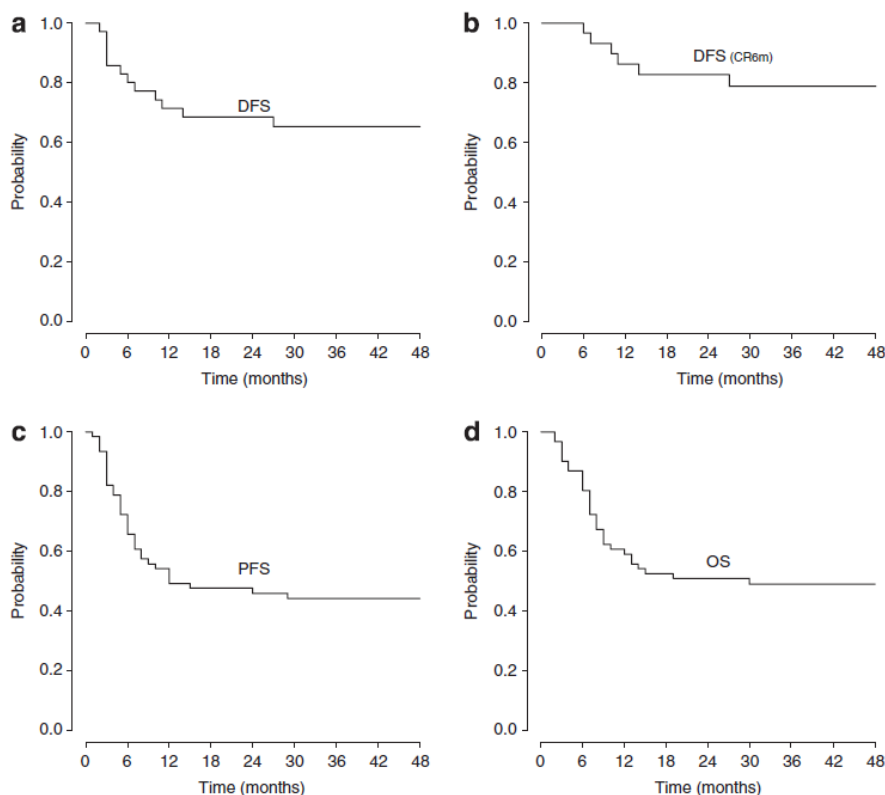
Overall response rate was 72%, with 18 of 25 patients responding (15 CR and 3 PR) to the complete treatment of 6 CHOP-AL courses. There were 6 early progressions during treatment and one early toxic death. In the context of the 18 responding patients, 7 maintained their response until the last follow-up, and 2 died of toxicity. Eight patients were alive at last follow-up.

Survival and prognostic factors

In the Clin A study, the 4-year OS, PFS and DFS rates were 49% (95% confidence interval (CI), 37–63%), 44% (95% CI, 33–58%) and 65% (95% CI, 51–83%), respectively (Figure 2). The DFS for patients maintaining the response for at least 6 months was 78% (95% CI, 65–95%).

Figure 2.

Clin A study: Kaplan–Meier survival curves: (a) DFS; (b) DFS of the Clin A trial for patients who maintained the CR for at least 6 months; (c) PFS; and (d) OS.



Univariate analyses were performed, regarding the impact of age, sex, performance status, IPI, PIT, histological subtype, extranodal disease and transplant type on outcome. On univariate analysis, gastrointestinal and liver involvement was associated with a shorter PFS (21 vs 51%, $P=0.035$), and there was a trend for shorter OS (26 vs 55%, $P=0.061$). In our population, the IPI and the PIT did

not achieve statistical significance for PFS and OS (IPI: 2 vs <2; PFS: 39 vs 58% ($P=0.22$); OS: 41 vs 62% ($P=0.16$)). We did not observe a significant difference in the outcome between the different histotypes. At 40 months of median follow-up, PFS and OS were as follows in different subtypes: 47 and 50% for PTCL-NOS; 36 and 54% for ALK negative, and 50 and 50% for AILD (Figure 1; Supplementary Information).

Survival outcomes after SCT were not significantly different, with a 4-year OS of 92% for autoSCT and 69% for alloSCT ($P=0.10$). Similarly, 4-year PFS was 70 and 69% for those receiving autoSCT or alloSCT ($P=0.92$), respectively (Figure 2; Supplementary Information). However, we must note that our study was not designed and powered to evaluate the differences between transplant types. On multivariable analysis (Table 2, Model 1), the achievement of CR maintained for at least 6 months had a dominant effect on PFS and OS, regardless of the patient's age, IPI or extranodal involvement. Patients who received a transplant had an advantage in OS (hazard ratio (HR)=0.04; 95% CI, 0.01–0.37, $P=0.004$ for autoSCT; HR=0.22; 95% CI, 0.07–0.67, $P=0.008$ for alloSCT; Table 2, Model 2).

Table 2 - Clin A: multivariable Cox model analyses of PFS and OS with clinical response (Model 1) or transplant (Model 2) as time-dependent variables. Clin B: multivariable Cox model analyses of PFS and OS with clinical response as the time-dependent variable.

	PFS Clin A			OS Clin A		
	HR	95% CI	P	HR	95% CI	P
Model 1						
Response CR6m vs CR/PR/PD	0.15	0.05, 0.39	0.0001	0.18	0.07, 0.48	0.0006
Patient's age (years) 58 vs 41 ^a	0.93	0.44, 1.95	0.456	0.90	0.41, 1.99	0.663
IPI ≥2 vs <2	1.03	0.42, 2.49	0.950	1.17	0.46, 2.97	0.743
Liver ± Gastrointestinal vs Others	1.33	0.62–2.86	0.460	1.19	0.53, 2.69	0.676
Model 2						
<i>Transplant</i>						
Auto vs no	0.51	0.14, 1.85	0.302	0.04	0.01, 0.37	0.004
Allo vs no	0.56	0.17, 1.79	0.326	0.22	0.07, 0.67	0.008
Patient's age (years) 58 vs 41 ^a	0.72	0.42, 1.23	0.227	0.83	0.49, 1.41	0.497
IPI ≥2 vs <2	1.36	0.59, 3.12	0.466	1.26	0.50, 3.15	0.620
Liver ± Gastrointestinal vs Others	1.80	0.85, 3.80	0.125	1.32	0.59, 2.96	0.499
		PFS Clin B			OS Clin B	
	HR	95% CI	P	HR	95% CI	P
Response CR6m vs CR/PR/PD	0.20	0.04, 0.91	0.038	0.05	0.01, 0.48	0.009
IPI >2 vs ≤2	0.96	0.34, 2.69	0.940	1.05	0.34, 3.22	0.930
Liver ± Gastrointestinal vs Others	1.90	0.69, 5.25	0.214	2.18	0.72, 6.65	0.169

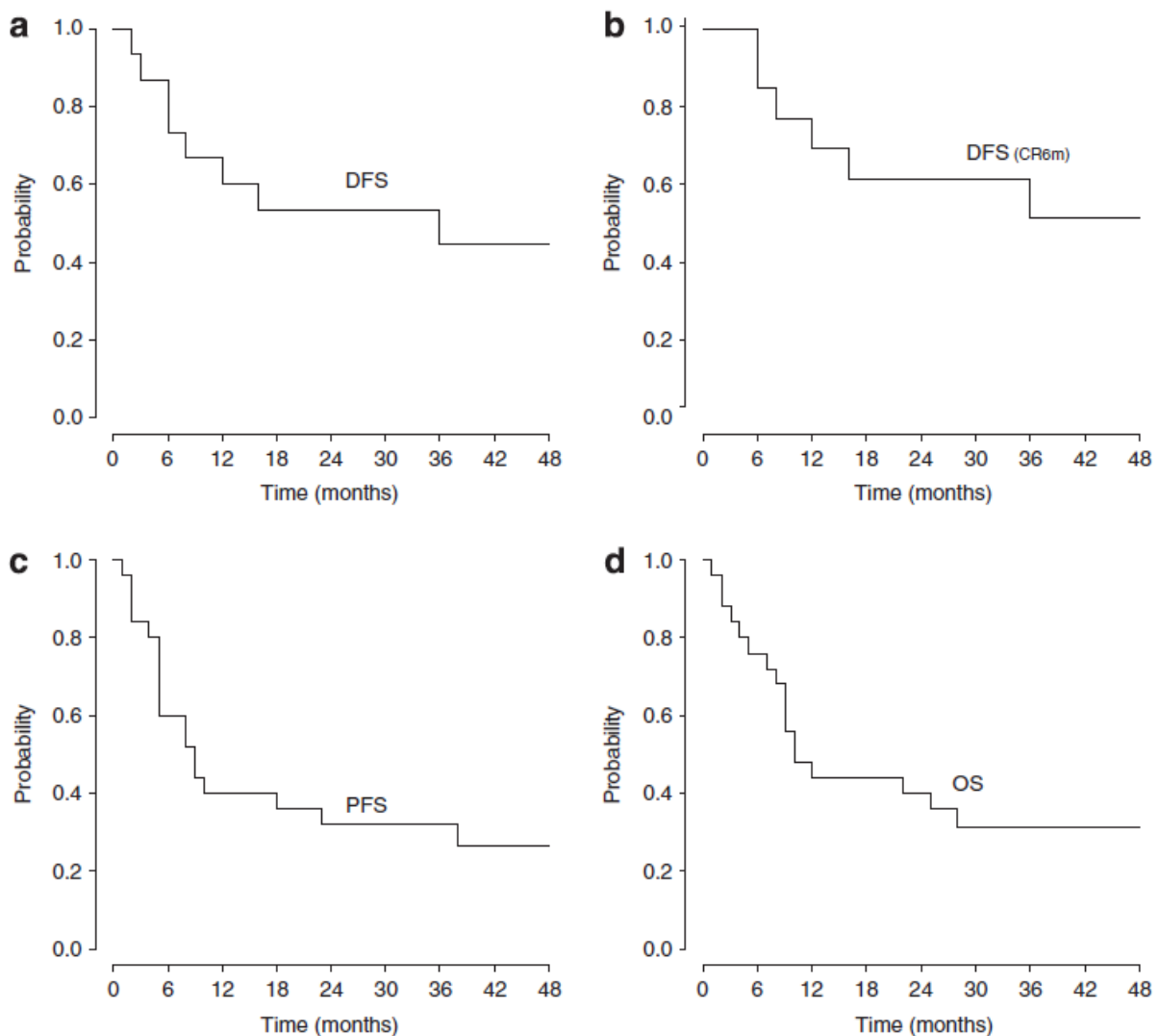
Abbreviations: allo, allogeneic stem cell transplantation; auto, autologous stem cell transplantation; CI, confidence interval; CR6m, complete remission maintained for at least 6 months; CR: complete remission not maintained for at least 6 months; extranodal, included disease in the liver and gastrointestinal tract; HR, hazard ratio; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial remission; IPI, International Prognostic Index.
^aThe two values are, respectively, the third and first quartiles of age distribution.

In Clin A, 8 of 61 patients died of treatment-related causes with a cumulative incidence of NRM of 13%; 5 died after HyperCHidam of infections ($n=4$) or multiorgan failure ($n=1$), whereas 3 died after alloSCT ($n=1$ encephalitis, $n=1$ GVHD, $n=1$ pneumonia).

In the Clin B study, the estimated 4-year OS, PFS and DFS rates were 31% (95% CI, 17–56%), 26% (95% CI, 13–52%) and 44% (95% CI, 24–80%), respectively (median follow-up of 48 months) (Figure 3). The DFS for the 13 patients maintaining the response for 6 months was 51.3% (95% CI, 29–89%). On univariate analysis, gastrointestinal and liver involvement was associated with a trend toward reduced PFS (4-year estimates: 14 vs 31%, $P=0.075$) and reduced OS (14 vs 38%, $P=0.034$). On multivariable analysis (Table 2), the achievement of a CR maintained for at least 6 months was the factor associated with the longest PFS (HR=0.20; 95% CI, 0.04–0.91; $P=0.038$) and OS (HR=0.05; 95% CI, 0.01–0.48; $P=0.009$).

Figure 3.

Clin B study: Kaplan–Meier survival curves: (a) DFS; (b) DFS of the Clin B trial for patients who maintained the CR for at least 6 months; (c) PFS; (d) OS.



In Clin B, 3 of 25 patients died of infectious complications (pneumonia ($n=2$) and cytomegalovirus (CMV) encephalitis ($n=1$)), resulting in a cumulative incidence of NRM of 12%. Considering the slow accrual and the high NRM with conventional dose chemotherapy, the Data and Safety Monitoring Board stopped the Clin B study.

Adverse events

Table 3 shows all grade 3–4 adverse events that occurred during the induction phase. Following CHOP-AL, we observed mainly hematological toxicity. CMV reactivation was described in 17 of 119 cycles (14%). Infectious complications were very common after the first (17 of 56) or the second (15 of 44) cycle of HyperCHidam. CMV reactivation was reported in seven and five patients receiving the first or second cycle of HyperCHidam, respectively.

Table 3 - Incidence and maximum severity of adverse events (grade 3–4).

Adverse event	CHOP-AL (1° Clin A) (n=61)	CHOP-AL (2° Clin A) (n=58)	HyperCHidam (1° Clin A) (n=56)	HyperCHidam (2° Clin A) (n=44)	CHOP-AL (Clin B) 128 cycles ^a
Neutropenia	29 (48%)	24 (41%)	56 (100%)	43 (98%)	50 (39%)
Thrombocytopenia	7 (11%)	4 (7%)	50 (89%)	39 (89%)	6 (5%)
Gastrointestinal	1 (2%)	2 (3%)	6 (11%) ^b	3 (7%)	3 (2%)
Hepatobiliary	0	0	3 (5%)	1 (2%)	0
Infections	2 (3%)	2 (3%)	17 (30%) ^c	15 (34%) ^d	10 (8%)
Nervous system disorders	1 (2%)	1 (2%)	3 (5%)	0	1 (0.7%)
Renal and urinary	0	0	1 (2%)	1 (2%)	0
Cardiac	0	0	1 (2%)	0	1 (0.7%)

Abbreviations: AL, alemtuzumab; CHOP, cyclophosphamide, adriamycin, vincristine, prednisone. ^aThe toxicity was evaluated on the total number of cycles. ^bIncluding one patient who died of mucositis followed by multiorgan failure. ^cTwo patients died. ^dTwo patients died.

In Clin B, severe infectious complications occurred in 10 of 128 cycles (8%). CMV reactivation was detected in 9 of 128 cycles (7%), and CMV disease was reported in one patient who died of CMV encephalitis.

Discussion

The background of the present study relies on previous studies accomplished by our group showing: (1) an improved response rate induced by the combination of CHOP and AL in PTCLs at diagnosis;⁶ (2) the feasibility of high-dose chemotherapy and up-front autoSCT;⁹ and (3) the role of alloSCT as an effective salvage treatment.^{14, 15} Thus, we designed a study in which chemo-immunotherapy was used both in young and in elderly patients with the aim of improving the overall response rate and thus the survival outcome. According to the donor availability, young patients received either alloSCT or autoSCT as a consolidation treatment. This study was the first that tested the feasibility and efficacy of front-line alloSCT in PTCL.

In PTCL, the treatment with an anthracycline-based therapy is associated with clinical remission in more than half of the treated patients; however, the prognosis remains poor with a 5-year survival of

30–35%.²⁵ Modifications to the CHOP-based chemotherapy include the addition of etoposide, bortezomib or immunotherapy. In a large retrospective study conducted by Schmitz *et al.*,³ CHOP plus etoposide improved EFS but not OS in young patients with normal lactate dehydrogenase levels. However, in this analysis most patients were affected by ALCL and had a low IPI. A recent phase II study evaluated the combination of bortezomib and CHOP; despite the high response rate, the 3-year PFS and OS were not better than historical controls using CHOP alone.²⁶ AL was given in combination with CHOP at various schedules and doses; the achievement of CR varied from 65 to 70%, although with a quite limited advantage in terms of EFS.^{6, 7, 8}

Despite the absence of phase III trials, the consolidation of response with autoSCT is commonly employed in the clinical practice and the evidence is mostly derived from phase II studies. The most recent prospective trials of up-front autoSCT reported a favorable outcome with 3-year PFS and OS ranging from 36 to 48% and from 48 to 56%, respectively.^{12, 13} Reimer *et al.* found a significant correlation between PIT and OS. D'Amore *et al.* identified ALK-negative histology as a favorable prognostic factor whereas bone marrow involvement, performance status and age were associated with poor outcomes.

Given the concern about NRM, first-line consolidation with alloSCT has been explored only in very few retrospective studies. Kanakry *et al.*²⁷ reviewed the outcomes of 44 patients allografted from haplo donors ($n=22$) or human leukocyte antigen-matched related donors ($n=20$). These authors observed a trend toward better PFS for alloSCT in first remission vs beyond first remission (2-year PFS: 53 vs 29%). Recently, Smith *et al.*²⁸ retrospectively analyzed the outcome of patients undergoing autoSCT ($n=115$) or alloSCT ($n=126$). This large registry study has some caveats, among which there is the inclusion of a limited number of patients transplanted at the first CR, and the enrollment of a large number of patients with ALCL histology without additional information regarding the ALK status. Despite these limitations, a number of observations emerged: (1) patients autografted at the first CR had a 3-year PFS of 58%; (2) one-third of patients allografted remained disease free despite being transplanted with relapsed disease; and (3) the higher incidence of disease relapse in the autoSCT group was balanced out by a higher NRM in the alloSCT group.

In Clin A, at the end of the induction phase the CR rate was 54%. The consolidation with alloSCT or autoSCT was effective, since the DFS at 4 years was 79% in the patients maintaining the CR for at least 6 months. In agreement with our previous study of up-front autoSCT,⁹ the only factor influencing the outcome was the achievement of a stable CR, regardless of IPI or PIT. With a median follow-up of 40 months, PFS and OS (44 and 49%, respectively) are in line with, but not higher than the best published data.^{12, 13} Although a formal comparison between the two transplantation strategies is not possible, no significant difference was found.

Despite the use of intensified chemo-immunotherapy, in the present trial 18 of 61 (30%) young patients did not undergo transplantation for progressive disease. A similar percentage is also described in other studies. This is rather disappointing and represents the main unmet clinical need in PTCLs. For future improvement, we may envisage three main areas: (1) prognostic factors and biomarkers, (2) molecular profiling for better diagnostic accuracy and (3) novel drugs.

Apart from patient-specific clinical factors (IPI and PIT) and tumor-specific characteristics (histotype, ki-67 expression 80%, expression of cytotoxic molecules), very few prognostic factors are currently available to identify poor prognosis patients early during their clinical course. A potential novel biomarker is based on the inactivating mutations of the Ten-Eleven translocation 2 that have been associated with a shorter PFS and OS.²⁹ Molecular profiling could be helpful, but the large-scale applicability remains a matter of debate.³⁰ There are novel active drugs:

bendamustine, pralatrexate, romidepsin and brentuximab-vedotin (only for CD30-positive T lymphomas) have been recently investigated in relapsed patients, with promising response rates.^{31, 32, 33, 34} Consequently, a possible aim of future studies will be the front-line introduction of novel agents in combination with chemotherapy and/or SCT.

Patients enrolled in the Clin B study were at high risk, due to an IPI of 2 and a PIT of 2–4. Our trial evaluated CHOP-21 and reduced AL dose for the first time in elderly patients, and demonstrated a clinically relevant toxicity with three treatment-related deaths. Despite an encouraging overall response rate (72%), the majority of patients relapsed, resulting in disappointing survival outcomes. Due to the high-relapse rate and significant toxicity, this study was closed prematurely by the Data and Safety Monitoring Board. Few data are available for the treatment of elderly patients. The study by Schmitz *et al.*³ reported the treatment of 90 patients over 60 years of age with CHOP or CHOEP at 2- or 3-week intervals. The outcome was not improved by dose-dense chemotherapy or by the addition of etoposide.

The goal of our intensified chemo-immunotherapy was to improve the response rate. This strategy was associated with some toxicity (13 and 12% for NRM in Clin A and Clin B studies, respectively). This finding can be explained by several factors: (1) patients affected by PTCLs have a profound disease-related immunodeficiency; (2) the administration of AL before the intensive chemotherapy most likely increased the infectious complications in the Clin A study (in fact, two doses of AL produced a profound decline in circulating T cells before the administration of high-dose chemotherapy); (3) the HyperCHidam regimen has been evaluated for the first time by Todeschini *et al.*¹⁹ in 28 patients affected by relapsed and refractory Hodgkin and non-Hodgkin lymphomas. In that group of patients, heavily pretreated, the authors described three toxic deaths and a high incidence of infectious complications. In our cohort of patients, pretreated only with two cycles of CHOP-AL, we observed five deaths after HyperCHidam. Therefore, we think that this combination of drugs and not only AL influenced the NRM; (4) even when used at a reduced dose, AL still causes serious immunodeficiency in elderly patients. The higher NRM reported in our study can not only be explained by the higher median age of the patients but also by the advanced

disease status (100% had IPI score 2) and by the poor performance status (32% had an eastern cooperative oncology group of 2 or 3); (5) although low, the alloSCT NRM was higher than that of conventional therapy or autoSCT, and this had an influence on OS.

In conclusion, our trial demonstrated several novel and important findings. First, AL cannot be safely associated with high-dose chemotherapy. AlloSCT or autoSCT can be used as a front-line treatment to consolidate the response and prolong DFS, but allografting is not yet indicated outside a clinical trial. In addition, low-dose AL in the elderly is still associated with relevant toxicity without a survival benefit.

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