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ORIGINAL ARTICLE

Oral fludarabine in combination with doxorubicin and dexamethasone as first-line therapy for nodal peripheral T-cell lymphomas: early results of a prospective multicenter study

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Abstract
Purpose Nodal peripheral T-cell lymphomas (PTCLs) have particularly poor prognoses. Few data enabling establishment of an accepted standard treatment modality for PTCLs are available. We hypothesized that fludarabine-based regimens are tolerable and effective in treatment for nodal PTCLs. Therefore, this study was to analyze the toxicity of, response rate for, and outcome of treatment for nodal PTCLs with oral fludarabine, doxorubicin, and dexamethasone (FAD).
Methods Patients with PTCLs received FAD every 28 days, consisting of oral fludarabine at 40 mg/m^2 on days 1–3, doxorubicin at 50 mg/m^2 on day 1, and oral dexamethasone at 20 mg/day on days 1–5. Patients who did not exhibit disease progression received at least four courses of treatment.
Results Thirty-one of 35 patients with previously untreated nodal PTCLs enrolled in the study from 2007 to 2008 were evaluable. The incidence of grade 3–4 neutropenia was 55%. Nine patients had to have dose reductions of fludarabine and doxorubicin, none of whom had grade 3 or 4 toxic effects at the lower dose. Five of 31 patients had pneumonitis. No treatment-related mortality occurred. The response rate for the entire patient population was 71%, and the complete remission rate was 48%. The PFS and OS rates at 2 years were 54.2 and 77.1%, respectively. Four patients had died of cancer progression at the time of this analysis. The serum lactate dehydrogenase level had a significant effect on PFS and OS.
Conclusion The FAD regimen had encouraging efficacy with an acceptable toxicity profile in patients with nodal PTCLs.

Keywords Chemotherapy · Fludarabine · Peripheral T-cell Lymphoma · Toxicity · Survival

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Introduction

Peripheral T-cell lymphomas (PTCLs) originate from mature post-thymic T cells. According to the proposed 2008 World Health Organization classification [1], PTCLs consist of 20 lymphomas grouped into leukemic, extranodal, and nodal types. Researchers have recognized an increasing number of subtypes of PTCLs. Angioimmunoblastic T-cell lymphoma (AITL), anaplastic large-cell lymphoma (ALCL), and PTCL, unspecified (PTCL-U) are

the most common forms of PTCLs and classified as nodal types. AITL and ALCL are unique subtypes of PTCLs, but PTCL-U includes all T-cell neoplasms that do not fit into any of the better defined subtypes [2]. Conclusive data on treatment for nodal PTCLs in the literature are lacking; however, nodal PTCLs are currently treated using the same approach as that for B-cell lymphoma. Cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) were commonly used in the first-line treatment for nodal PTCLs but seemed to be inadequate [3]. The complete remission (CR) rate for CHOP was highly variable, and most patients who received CHOP had refractory disease or relapses in less than 1 year [3]. In another study, the 5-year disease-free survival rate for CHOP or CHOP-type regiments was less than 30% in a large series of patients with PTCLs [4]. Indeed, these results indicate that a drug or regimen that is active against B-cell lymphoma will not necessarily be active against PTCLs.

Whether high-dose chemotherapy followed by autologous peripheral blood stem cell transplantation (PBSCT) is beneficial as first consolidation treatment for nodal PTCLs is controversial. Significant numbers of patients with nodal PTCLs in previous prospective trials had disease that was refractory to induction therapy and did not undergo autologous PBSCT except for anaplastic lymphoma receptor tyrosine kinase (ALK)-positive ALCL [5, 6]. Additionally, relapse remains the leading cause of treatment failure after autologous PBSCT in nodal PTCLs cases [7]. Investigators have frequently examined the use of allogeneic hematopoietic stem cell transplantation (HSCT) in patients with PTCLs, with encouraging results for relapsed and/or refractory cases in small series. Although the PFS was prolonged for allogeneic-HSCT trial, the overall survival rate does not improved when compared to the OS rates of the patients treated with PBSCT, because there were significant non-relapse-related mortality rates in patients receiving full myeloablative allogeneic transplants [8]. Also, the use of allogeneic HSCT should be accompanied by finding matched donors and to find the matched donors was not considered fairly easy in appropriate periods. Corradini et al. [9] reported on a pilot study of reduced-intensity conditioning pretreatment followed by allogeneic HSCT for nodal PTCLs. They found that this approach was effective and can be considered as consolidation treatment for nodal PTCLs after first-line therapy. Of note is that achievement of CR before performing HSCT is a strong predictor of good survival. Obviously, intensive treatment strategies and/or non-cross-resistant therapies are greatly needed early in the course of nodal PTCLs [7].

Researchers are studying several new agents that have exhibited activity against cutaneous T-cell lymphoma and T-cell leukemia in treatment for systemic PTCLs. One of these agents is fludarabine, which is a purine analog and approved for the treatment for low-grade lymphoid malignancies. Preliminary data from case reports suggested that it was effective and safe in patients with PTCLs, even those with refractory disease [10, 11]. Rossi et al. [12] suggested that the effect of oral fludarabine on the treatment for indolent lymphoma was equivalent to that of intravenous fludarabine and that the former was more tolerable in that it decreased the incidence of neutropenia, thrombocytopenia, and infection [13]. Moreover, physicians have commonly used anthracyclines to treat B-cell non-Hodgkin lymphoma (NHL) and found that they seemed to be active in PTCL cases. Combinations of oral fludarabine and anthracyclines seemed to be synergistic in treating NHL. However, the reported data on the treatment for PTCLs with these combinations are scarce. Based on the above-mentioned considerations, we hypothesized that fludarabine-based regimens are tolerable and effective in treatment for nodal PTCLs**.** We, therefore, performed a phase II clinical trial of oral fludarabine, doxorubicin, and dexamethasone (FAD) as first-line therapy for nodal PTCL to preliminarily assess its toxicity and efficacy. The FAD regimen had encouraging efficacy with an acceptable toxicity profile in 31 patients with nodal PTCLs.

Patients and methods

Disease evaluation

Thirty-five patients with previously untreated nodal PTCLs enrolled in the study from 2007 to 2008 were reviewed by two expert pathologists for diagnostic confirmation and categorization of these patients according to the 2008 World Health Organization classification [1]. PTCL-U was diagnosed according to the expression of CD45 and/or one or more pan-T-cell antigens (CD45RO, CD2, CD3, CD5, and CD7) in tumor cells. ALK-negative ALCL was diagnosed according to the expression of CD30 with variable loss of expression of CD2, CD3, and/or CD5 and frequent expression of cytotoxic proteins (granzyme B, TIA-1, and perforin) in tumor cells and $CD43^{+/-}$, $CD45RO^{+/-}$. AITL was diagnosed according to the expression of CD45, CD10, CXCL13, and one or more pan-T-cell markers (CD2, CD3, CD5, and CD7) in tumor cells. Rearrangements of T-cell receptor β and/or γ confirmed the monoclonality of PTCLs. The pretreatment evaluation consisted of complete blood cell counts, routine chemistry measurements (including that of serum lactate dehydrogenase [LDH] levels), chest and abdominal computed tomography scans, bone marrow examinations, and other tests when clinically indicated. The disease stage was determined using the Ann Arbor criteria, and all patients were evaluated for the presence of risk factors for NHL according to the International

Prognostic Index based on age, stage, performance status, number of extranodal disease sites, and serum LDH level.

Eligibility criteria

PTCLs must be diagnosed using histological biopsy, immunohistochemical analyses, and cytogenetic assessment. Our trial was approved by the Ethics Committee or an equivalent at each participating center, and each patient gave his or her written informed consent to participate in the study. Patients with PTCL-U, AITL, or ALK-negative non-skin-type ALCL were included in the study. Their ages ranged from >18 to <75 years, and they were required to have previously untreated disease, negative human immunodeficiency virus tests, performance status scores no higher than 2 according to the Eastern Cooperative Oncology Group criteria, estimated survival durations greater than 3 months, and normal pulmonary and cardiac function. Also, female patients could not be pregnant. Patients with impaired renal (serum creatinine level greater than the upper limit of normal), hepatic (bilirubin level greater than the upper limit of normal), and/or hematopoietic (absolute neutrophil count [ANC] $< 1.5 \times 10^9$/L and/or platelet count $<80 \times 10^9$/L) function were excluded unless the impairment was considered to have resulted directly from their lymphoma. In addition, patients with severe peptic ulcerations or lymphoma involving the central nervous system were excluded.

Treatment

Every 28 days, patients received FAD, which consisted of oral fludarabine (Fludara Oral; Bayer Schering Pharma AG, Berlin, Germany) at 40 mg/m^2 on days 1–3, doxorubicin (Adriamycin; Pfizer Pharmaceuticals, New York, NY) at 50 mg/m^2 on day 1, and oral dexamethasone (Shandong Xinhua Pharmaceutical Co. Ltd., Zibo, People's Republic of China) at 20 mg/day on days 1–5. Patients who did not exhibit disease progression received at least four courses of treatment. In each treatment cycle, the patients did not undergo irradiation unless they had organ dysfunction that may have been life-threatening because of the presence of a bulky mass. Patients in CR or unconfirmed CR (CRu) received four further treatment cycles followed by irradiation at sites of bulky masses. Autologous stem cell transplantation was permitted in patients with high or high-intermediate International Prognostic Index after completion of chemotherapy.

Chemotherapy was withheld for 1 week at the beginning of next cycle of chemotherapy until the ANC was greater than 1.5×10^9/L and platelet count was greater than 100×10^9/L. If a patient's ANC or platelet count did not reach the threshold level after the 1-week delay, and treatment was delayed for another week. If the counts still were below the threshold levels after 2 weeks but the ANC was greater than 1×10^9/L and the platelet count was greater than 75×10^9/L or if febrile neutropenia or grade 4 neutropenia lasting more than 7 days occurred at any time, the doses of fludarabine and doxorubicin were reduced by 50% in the subsequent course. Patients with ANCs lower than 1×10^9/L and/or platelet counts lower than 75×10^9/L after the 2-week delay were removed from the study.

Prophylactic use of granulocyte colony-stimulating factor (G-CSF) and anti-infective agents (antifungal, antiviral, and anti-pneumocystis carinii pneumonia [PCP] agents) was not permitted in this phase II trial. However, if a patient had grade 4 neutropenia or febrile neutropenia that lasted more than 7 days at any time during the first cycle of FAD, prophylactic G-CSF could be given in subsequent cycles. Therapeutic use of G-CSF was considered after the second cycle of treatment if the ANC did not reach the threshold level. Use of dipyridamole and other inhibitors of adenosine uptake in PTCLs patients for treating complicated disease were avoided [14]. All blood products required for supportive treatment were irradiated at a minimum of 25 Gy. Any significant pleural effusions or abdominal ascites were drained completely prior to initiation of therapy with fludarabine.

Statistical analysis

This trial was a multicenter, open-label, single-arm phase II investigation. We excluded four patients from the 35 enrolled patients because they withdrew their consent before the initiation of treatment**.** A two-stage design as described by Simon [15] was used. If observed evidence indicated that the true underlying overall response rate (CR/CRu/partial remission [PR]) was at least 40%, then further testing of FAD was considered. The planned accrual in the first stage was 10 assessable nodal PTCLs patients. An early stopping rule was used so that if fewer than four responses were observed in the first 10 patients, the trial would be terminated with the conclusion that there was little evidence suggesting that the overall response rate would reach 40%. However, if at least four responses were observed in the first 10 patients, the study would continue to accrue a total of 31 patients. FAD was considered to be worth for further investigation if at least 16 of the 31 patients exhibited responses to it. This dosing provided 70% statistical power to detect a difference of 18% with a significance level less than 0.1 (type 1 error) when compared with conventional chemotherapy (CHOP or CHOP-like regimens) in enrolled patients. The trial was designed to accrue a maximum of 31 patients over 2 years.

CR was defined as the complete disappearance of all detectable clinical and radiographic evidence of disease

and of all disease-related symptoms if present before therapy. CRu indicated that the sum of the products of the greatest diameters (SPD) of a residual lymph node mass and/or individual nodes decreased by more than 75% when compared with the SPD of the original mass. PR indicated a decrease in the SPD of up to the six largest dominant nodes or nodal masses of at least 50%. Progressive disease denoted any increase in the SPD of any measurable lesions of at least 25% and/or appearance of new lesions. Patients who did not meet the criteria for PR or progressive disease were classified as having stable disease.

Radiological examination for each patient was scheduled after the completion of every two courses of treatment. For the patients with CR or CRu, the efficacy of FAD had to be confirmed 28 days after the completion of every two courses of treatment.

The primary end point of the study was the tolerability of FAD according to the toxicity-related death rate and toxic effects. Toxicity was assessed in each cycle according to National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0). The secondary end points were progression-free survival (PFS) and OS. The OS duration was measured from the date of study entry to the date of death of any cause. The PFS duration was measured from the date of initiation of treatment to the date of first instance of progressive disease or relapse. Tumors were measured every 3 months over the first 2 years of the study and every 6 months thereafter over the follow-up period. The closing date for the planned first analysis of results was 41.6 month after the initiation of the study. The survival analysis results are presented in Kaplan–Meier survival graphs. All valuable data are reported for the intent-to-treat patient population, and the statistical data were obtained and analyzed using the SPSS software program (SPSS Inc., Chicago, IL) and/or PASS 2008 software program (version 08.0.13; NCSS, Kaysville, UT).

Results

Patient characteristics

Thirty-one of 35 patients with previously untreated nodal PTCLs enrolled in the study from August 2007 to August 2008 were evaluable. We excluded four patients from the analysis because they withdrew their consent before the initiation of treatment. The patients were enrolled in four centers in the People's Republic of China. The patients' pretreatment characteristics are summarized in Table 1. The majority of the patients were men, and the median age was 58 years (range 33–81 years). In total, the patients received 129 FAD chemotherapy cycles, and each patient received an average of 4.16 cycles. Twelve patients received 4 cycles, and ten patients received more than 4 cycles. Others received less than 4 cycles but more than 2 cycles. All patients were in line with the intent-to-treat patient population according to the protocol of the trial. The tumor types were PTCL-U, AITL, and ALCL in 22, 5, and 4 patients, respectively. Seventeen patients (55%) had an elevated serum LDH level (10% above the upper limit of normal).

Table 1 Characteristics of patients with nodal PTCLs treated with FAD

Characteristics	Eligible patients ($n = 31$)	
	N	%
Sex		
Male	19	61
Female	12	39
Age (years)		
Median	58	–
Range	33–81	–
Histologic subtype		
PTCL-U	22	71
AITL	5	16
ALK-negative ALCL	4	13
Stages		
I	2	6
II	9	29
III	11	35
IV	9	29
B symptoms	13	42
ECOG performance status		
0–1	25	81
2–3	6	19
Bulky disease	1	3
Elevated serum LDH level	17	55
IPI		
Low	12	39
Low—intermediate	6	19
Intermediate–high	8	26
High	5	16

ECOG Eastern cooperative oncology group and *IPI* international prognosis index

Toxicity

Hematological and pulmonary effects were the most common toxic effects of FAD (Table 2). Grade 3–4 neutropenia and thrombocytopenia occurred in 17 patients. Eleven patients received therapeutic G-CSF. A total of 28 cycles of treatment involved the use of G-CSF. Five patients had pneumonitis: three had mild bilateral interstitial infiltrations, whereas two had acute bronchitis.

Table 2 FAD toxicity

Toxic effects	*N* (%)	
	Any grade	Grade 3–4
Hematological	31 (100)	17 (55)
Hemoglobin level	10 (32)	0 (0)
Neutrophil count[a]	31 (100)	17 (55)
Platelet count	6 (19)	2 (6)
Non-hematological		
Fatigue	20 (65)	2 (6)
Nausea/vomiting	31 (100)	0 (0)
Diarrhea	2 (6)	0 (0)
Neurological	2 (6)	0 (0)
Skin rash	1 (3)	0 (0)
Alopecia	25 (81)	3 (10)
Pneumonitis[b]	5 (16)	3 (10)

[a] Seven patients had neutropenic fever

[b] Previously diagnosed as chronic bronchopneumonia

Pulmonary toxic effects always developed in patients previously having been diagnosed with chronic bronchopneumonia. The chemotherapy delayed in these five patients when diagnosed with pneumonitis. Prophylactic anti-infective agents were not used in all patients; however, these five patients with pneumonitis received broad spectrum antibiotics and/or antifungal regimens therapy. Three patients who had pulmonary interstitial infiltrations received another 20 mg of prednisone three times a day. The pulmonary toxic effects disappeared 1 week after using antibiotics and/or antifungal regimens therapy in patients who had pneumonitis. All of the patients who had pneumonitis experienced complete recovery from antibiotics and/or antifungal therapy even after tapering of prednisone and continued to receive chemotherapy. Seven patients had to have treatment delays. A total of 16 cycles involved the treatment delay due to the hematological and/or pulmonary toxicity. Nine patients had to have FAD dose reductions due to the hematological and/or pulmonary toxicity. Toxicity of FAD was reduced in these nine patients, and none of them had grade 3 or 4 toxic effects while receiving the reduced doses (reduced by 50% according to the protocol). Other non-hematological toxic effects were generally mild. Also, we observed no treatment-related mortality. Of note is that prophylactic use of G-CSF and antifungal, antiviral, and PCP agents was not permitted.

Response to therapy and survival

The response rate for FAD in the 31 patients was 71% (22/31), and the CR rate was 48% (15/31). The response rates in the PTCLs, AITL, and ALCL cases were 73, 100, and 25%, respectively. Four of the patients with AITL exhibited CR (Table 3); these four patients were alive at the time of the last follow-up visit. The median follow-up duration in the surviving patients was 27 months (range, 8.1–41.6 months). The median PFS duration was 25.9 months for all patients, whereas the median OS duration had not reached at the point of last follow-up. The 2-year PFS and OS rates were 54.2 and 77.1%, respectively (Fig. 1). The estimated median PFS durations in the PTCL-U, AITL, and ALCL cases were 28.0, 20.0, and 8.9 months, respectively. Two patients with PTCL-U, one with AITL and one with ALCL, had died of cancer progression at the time of this analysis. Overall, extranodal involvement and serum LDH level significantly affected PFS in univariate analyses of the intent-to-treat patient population (Kaplan–Meier estimate; $P = 0.023$ and $P = 0.003$, respectively [log-rank test]). LDH level even had a significant effect on OS ($P = 0.004$). Patient age greater than or less than 60 years old did not affect PFS or OS (Fig. 2). Three patients who did not have responses to FAD received other treatments: two received CHOP and one received mitoxantrone, isophosphamide, and etoposide. All three died within 6 months after initiation of the study. Nine limited stage patients in our study group received radiation therapy after completion of FAD chemotherapy. Meanwhile, only 2 patients who had relapsed disease during the follow-up period received high-dose chemotherapy followed by ASCT.

Discussion

In this article, we report the early results of a prospective multicenter study designed to analyze the toxicity of, response rate for, and outcome of FAD in patients with

Table 3 Response to FAD by nodal PTCLs subtype

Diagnosis	No. of patients	*N* (%)			
		CR	PR	CR + PR	PD
Total	31	15 (48)	7 (23)	22 (71)	3 (10)
PTCL-U	22	11 (50)	5 (23)	16 (73)	2 (9)
AITL	5	4 (80)	1 (20)	5 (100)	0 (0)
ALK-negative ALCL	4	0 (0)	1 (25)	1 (25)	1 (25)

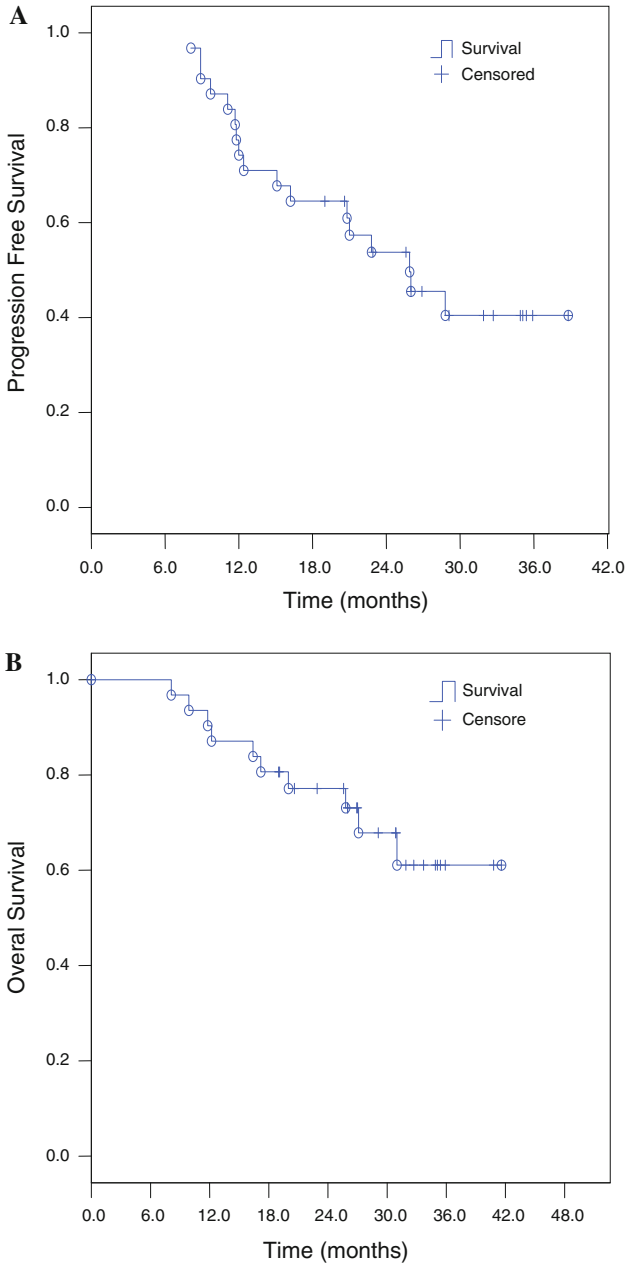

Fig. 1 Overall survival (OS) and progression-free survival (PFS) durations in all patients who received FAD (oral fludarabine, Adriamycin, and dexamethasone): **a** The estimated 2-year PFS rate was 54.2%, and the median PFS duration was 25.9 months. **b** The 2-year OS rate was 77.1%, and the median OS duration had yet to be reached at the time of analysis

nodal PTCLs, consisting of PTCL-U, AITL, and non-skin-type ALK-negative ALCL. FAD was active and feasible in patients with non-pretreated nodal PTCLs. The regimen had an acceptable toxicity profile and resulted in longer PFS and estimated OS durations than in some reported studies.

In our study, we considered ALCL to be nodal PTCLs. A recent study showed that ALK-positive ALCL is clinically and immunophenotypically different from ALK-negative ALCL [16]. Except for those with ALK-positive ALCL, patients with nodal PTCLs tend to present with disease in extranodal sites and generally have poorer prognoses than do those with aggressive B-cell NHL. Therefore, we excluded patients with ALK-positive ALCL from our study.

Most reported studies have shown that CHOP is not a successful treatment for PTCLs [17]. Moreover, the impact of high-dose chemotherapy with autologous HSCT as early consolidation therapy for nodal PTCL has been controversial. Therefore, more intensive treatment strategies or better non-cross-resistant therapies are greatly needed for early-stage PTCL [7]. At present, conclusive data in the literature on the effectiveness of front-line treatment for nodal PTCLs are lacking; thus, a clinical trial is always recommended for patients with nodal PTCLs according to the National Comprehensive Cancer Network guidelines of oncology. The literature contains relatively little information about fludarabine-, anthracycline-, and steroid-containing chemotherapy regimens as first-line therapy for NHL, especially for PTCLs. Therefore, we performed this phase II clinical trial of FAD in patients with nodal PTCLs.

In terms of the tolerability of FAD, our results are consistent with other published data indicating that hematological and pulmonary toxic effects are the most common toxic effects of fludarabine-containing regimens [18, 19]. Although all of the patients in our study reported at least first-level adverse event, most of the events were considered manageable. Seventeen patients had grade 3–4 hematological toxic effects, all of whom experienced complete recoveries from these effects and continued to receive chemotherapy. Also, pulmonary toxic effects were more likely common in patients previously diagnosed with chronic bronchopneumonia. This phenomenon was different from that described by Helman et al. [20] who showed that pulmonary toxic effects in patients receiving fludarabine-containing regimens had nothing to do with a history of underlying lung disease. However, our sample size was limited, and the data that describe that pulmonary toxic effects were more likely common in patients previously diagnosed with chronic bronchopneumonia are scarce. Thus, more investigations of this phenomenon in clinical trials are recommended.

Treatment for nodal PTCLs remains unsatisfactory [21]. Response rates for CHOP have ranged from 50 to 60% in patients with PTCL-U, but the disease-free survival has been poor, with a 5-year OS rate less than 30% [22]. Because of these poor results, researchers have examined other regimens as primary induction therapy for PTCL, such as hyper-cyclophosphamide, vincristine, Adriamycin, and dexamethasone (hyper-CVAD); Lymphoma non-Hodgkin (LNH) programs by French Groupe d'Etude des

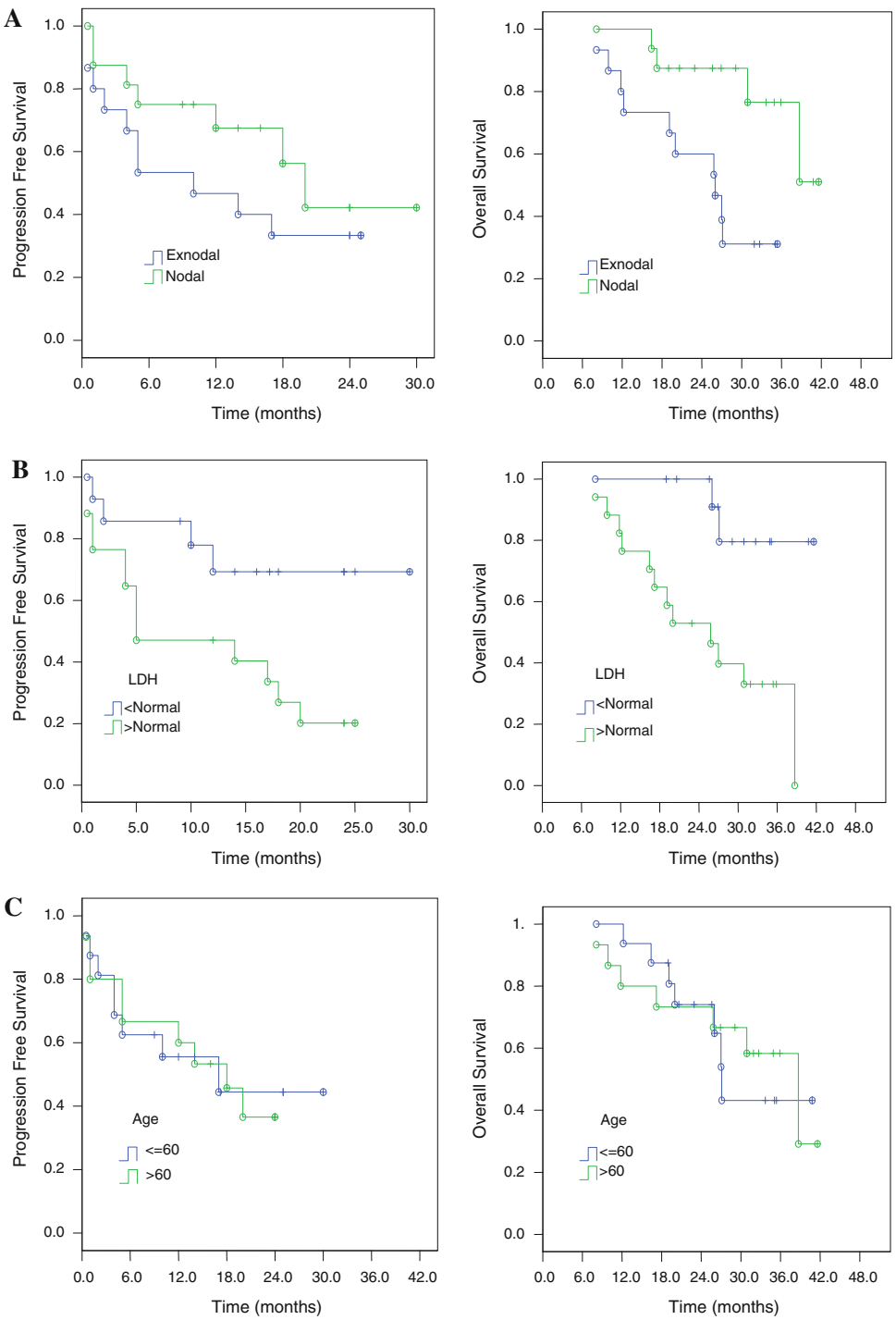

Fig. 2 The progression-free survival (PFS) and overall survival (OS) by **a** extranodal involvement ($P = 0.023$ and $P = 0.003$, respectively), **b** serum lactate dehydrogenase (LDH) level ($P = 0.082$ and $P = 0.004$, respectively), and **c** patient age ($P = 0.230$ and $P = 0.812$, respectively)

Lymphomes de l'Adulte (GELA); and regimens containing platinum compounds. The results for these regimens were not better than those for the standard CHOP regimen [23]. Outcomes for these regimens in patients with AITL and ALCL were similar to those in patients with PTCL-U. Moreover, most studies of the treatment in nodal PTCLs were retrospective analyses and included different PTCL histologies. Therefore, drawing definitive conclusions about which is the best choice for treatment for nodal PTCLs is very difficult.

FAD regimens have been active against indolent lymphoma [24]. In addition, purine analogs have exhibited some single-agent activity against PTCLs [11, 25, 26]. Fludarabine can be incorporated into the DNA of dividing cells and can even kill non-dividing (G0-phase) cells [27, 28]. Authors have reported that fludarabine was

effective and safe in treatment for PTCLs, even in refractory cases, [10, 11], and these results seemed to indicate that fludarabine, to a certain extent, has the more potential of overcoming drug resistance when compared to other commonly used cytotoxic drugs. Oral fludarabine had an equivalent effect on indolent lymphoma compared to that of intravenous fludarabine and had more favorable tolerability by decreasing the incidence of neutropenia, thrombocytopenia, and infections [12]. The present study related the results of use of oral fludarabine in the treatment for PTCLs.

We have not performed a controlled clinical trial to assess the efficacy and toxicity of FAD compared with that of conventional CHOP in patients with nodal PTCLs. This limitation did not affect us to draw the preliminary conclusion as the end point of this trial was concerned. Additionally, three aspects of reasons why we have not performed a controlled clinical trial can be addressed. The first is that we did not consider CHOP to be successful in treating PTCLs or consider CHOP as standard criterion for this group of patients. The second was related to the fact that our sample size was limited. The third was that we focused on the tolerability and outcomes of FAD instead of comparing FAD with CHOP.

The CR rate of 48% in our trial was equivalent to rates reported in the literature. In one retrospective trial in particular, the CR rate was 44% [29]. In patients with AITL, our study showed CR rate of 80%, more than most other studies. At the median follow-up duration of 27 months, our results were encouraging, because the PFS and OS were better than those in similar published retrospective studies. Based on above-mentioned results, it is worth to do further investigation into large-scale studies. Generally, the results of the present preliminary study compare favorably with those of most published studies of treating nodal PTCLs despite the fact that the median OS had not been reached at the last follow-up [29–35]. Future controlled trials using FAD for the treatment for PTCLs are recommended.

In conclusion, FAD was active and feasible in patients with non-pretreated nodal PTCLs. The regimen had an acceptable toxicity profile and resulted in longer PFS and estimated OS durations than in some reported studies. Prophylactic use of antifungal, antiviral, and PCP agents should be considered in patients with previously diagnosed chronic bronchopneumonia. A study with a longer follow-up period is required to better define the outcomes of FAD-based treatment for PTCLs, and we will carry out further controlled studies of FAD regimens in the treatment for PTCLs in the future.

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Conflict of interest The authors declare that they have no conflict of interest.

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