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Fludarabine phosphate–CVP in patients over 60 years of age with advanced, low-grade and follicular lymphoma: A dose-finding study

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Abstract

The aim of this study was to establish a safe and effective regimen of fludarabine phosphate, cyclophosphamide, vincristine and prednisone (F–CVP) as first-line treatment for elderly patients with advanced, low-grade non-Hodgkin's lymphoma. Twenty-three patients >60 years were assigned successively to eight treatment cycles (Dose level 1: low F, low CV [$n = 4$]; 2A: high F, low CV [$n = 8$]; 2B: low F, high CV [$n = 4$]; 3: high F, high CV [$n = 7$]). High and low levels were: F, 25 and 20 mg/m^2, respectively (Days 1–5); C, 750 and 500 mg/m^2, respectively (Day 1); and V, 1.4 and 1 mg/m^2, respectively (Day 1). Patients received P at 40 mg/m^2 on Days 1–5. Response was assessed after Cycles 2, 4, 6 and 8. At level 3, dose-limiting toxicity (opportunistic infections and neutropenia) became evident, particularly after Cycle 6. Further patients were recruited at Dose level 2A. All regimens proved effective, with an OR rate of 78% (65% CR), and 3-year survival of 65% (±10%). Among 18 responders, 51% were still in response at 3 and 5 years. The study shows that this combination therapy is highly effective. The addition of F to CVP at Dose level 2A was feasible and increased the CR rate, with good tolerability in elderly patients.

Keywords: Fludarabine phosphate; Non-Hodgkin's lymphoma; Follicular lymphoma

1. Introduction

Elderly patients with advanced, low-grade and follicular non-Hodgkin's lymphoma (NHL) have incurable disease with poor prognostic factors at the time of diagnosis [1,2]. For asymptomatic patients, a 'wait-and-see' approach does not appear to modify the prognosis [3–5]. In symptomatic patients, conventional chemotherapy, based on alkylating agents, is ineffective in the long term [6], and more successful treatment strategies are needed.

Single-agent fludarabine phosphate (Fludara®) is a safe and effective therapy for NHL [7–10], and is well tolerated in elderly patients [11]. As a front-line therapy, fludarabine phosphate can achieve overall response rates (ORRs) of up to 84% [12], with good complete response (CR) rates (from 34% to 47%) [10–13]. Particularly high CR rates have been recorded in patients with follicular lymphoma (up to 60% in one trial) [12]. Fludarabine phosphate provides a good basis for combination therapies because of its more acceptable safety profile in comparison with alkylating agents [14]. Additionally, *in vitro* data support a synergistic effect of fludarabine phosphate and alkylating agents when used in combination [15,16].

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The combination of cyclophosphamide, vincristine and prednisone (CVP), with its good tolerability profile [17,18], is a standard chemotherapy for lymphomas. In the most recent trials, ORRs ranged from 53% to 83%, with 17–45% CR rates [13,17,18] and poor overall survival [18].

Fludarabine phosphate is currently under investigation, in combination with cyclophosphamide, to evaluate its potential for further improving response rates [19–23]. One such study has demonstrated that a dosing schedule of fludarabine phosphate (20 mg/m^2/day for 5 days) can be delivered in combination with a single dose of cyclophosphamide (1000 mg/m^2 for 1 day), with acceptable toxicity. The 27 patients recruited for this study achieved an ORR of 100% (87% CR) and an estimated 5-year overall survival of 63% [24].

These results provide a good rationale for the use of fludarabine phosphate in combination with CVP (F–CVP). Here, we describe a dose-finding study to ascertain a safe combination of F–CVP in patients over 60 years of age with advanced-stage, low- or intermediate-grade NHL.

2. Patients and methods

2.1. Patient population

This was a phase I/II dose-finding study, carried out at the Institute Bergonié, Bordeaux, France. Patients with low-grade NHL (working formulation groups A, B and C) or intermediate-grade NHL (groups D and E), *i.e.*, follicular; mantle cell; lymphocytic and marginal zone lymphomas, according to the WHO classification [25], were eligible for inclusion. All patients had advanced disease (stage III or IV), according to the Ann Arbor staging system. All patients were >60 years of age, with a WHO performance status of 0–2, and had not received prior chemotherapy. Patients with a prior history of severe cardiac, pulmonary, neurologic, psychiatric or metabolic disease were excluded, as were those with a calculated creatinine clearance of <40 ml/min [26], leukocytes $<3\times10^9$/l and platelets $<100\times10^9$/l. Patients with an alkaline phosphatase or bilirubin level more than twice the upper limit of the normal value were also excluded, unless this abnormality was clearly related to NHL. Finally, patients with prior malignancies (except non-melanoma skin tumour and *in situ* cervical carcinoma), or any unstable, pre-existing, major medical condition or HIV-positivity, were also excluded.

Pre-treatment evaluations included assessment of the patients' medical history, a general physical examination and measurement of all affected regions, including liver and spleen. Laboratory tests included measurement of full blood counts, CD3, CD4 and CD8 counts, and determination of the CD4/CD8 ratio. Tests of liver, kidney and cardiac function were performed, together with lymph node and bone marrow aspiration and biopsy. All patients provided informed, written consent prior to enrolment.

2.2. Dose and administration

Four dose levels were tested, each on four patients, as outlined in Table 1. Dose escalation was not performed within the same patient. Fludarabine phosphate was administered as a 30-min intravenous (iv) infusion, and a maximum of eight cycles of treatment were given. Prophylaxis against *Pneumocystis carinii* pneumopathy (PCP) was not mandatory. However, the occurrence of any episode of PCP during the trial would have led to the systematic use of PCP prophylaxis in all subsequent patients enrolled.

Enrolment of patients into the next dose-level group was dependent on the absence of unacceptable toxicity at the previous dose level. Grade 4 haematological adverse events, haemorrhage, nausea and vomiting, or constipation were classified as unacceptable toxicity. Grade 3 or 4 toxicity, as indicated by laboratory evaluations of bilirubin and alkaline phosphatase levels, urine analyses and full blood counts, was also considered unacceptable. If any single adverse event of the type described above was noted, patient accrual was continued into the group receiving the next step-up in dose. However, if two or three toxicities were observed, accrual continued at the same dose level. If the number of toxicities exceeded four, accrual reverted to the previous dose level. Dose levels 2A and 2B were considered equivalent, and were dependent upon toxicity results from the first step in dose (Dose level 1). Furthermore, progression to Dose level 3 required completion of the above criteria in Dose levels 2A and 2B. Accrual into the elevated dose levels was possible only if all four patients from the previous dose group were evaluable and had completed at least three courses.

Dose modifications were carried out in the event of haematological or non-hematological toxicity (Tables 2 and 3). Treatment was withheld in the event of grade 2 or 3 non-hematological adverse events, until the symptoms (which excluded nausea or vomiting, diarrhoea, hair loss, neurotoxicity and haemorrhage) resolved. If toxicity persisted beyond 2 weeks, treatment was discontinued.

Evaluations were repeated prior to each treatment cycle. Blood counts were taken on Days 8, 11, 14, 17, 20 and 23 of each cycle.

2.3. Treatment evaluation

Responses were evaluated using clinical and radiological criteria [27], including a computed tomography scan, prior to Cycles 3, 5 and 7, and complete re-staging

Table 1
Dose schedules

Dose level	Drug	Dose (mg/m^2/day)	Administration route	Day(s)
Dose level 1	F	20	iv	1–5
	C	500	iv	1
	V	1	iv	1[a]
	P	40	oral	1–5
Dose level 2A	F	25	iv	1–5
	C	500	iv	1
	V	1	iv	1[a]
	P	40	oral	1–5
Dose level 2B	F	20	iv	1–5
	C	750	iv	1
	V	1.4	iv	1[a]
	P	40	oral	1–5
Dose level 3	F	25	iv	1–5
	C	750	iv	1
	V	1.4	iv	1[a]
	P	40	oral	1–5

[a] 2 mg maximum.

including bone marrow biopsy if initially positive, at the end of treatment (performed between 3 and 5 weeks post-treatment). Treatment was discontinued in patients with disease progression.

CR was defined as the complete disappearance of all disease-related symptoms and measurable lesions, including those in the bone marrow. In patients with persistent, enlarged lymph nodes, active residual disease was confirmed by biopsy and cytology.

A decrease of at least 50% in the product of the two largest perpendicular diameters in all measurable lesions, with a disappearance of disease-related symptoms, was defined as a partial response (PR). In addition, positive or negative bone marrow biopsies were used to distinguish PR subtypes.

Progressive disease (PD) was defined as an increase of at least 25% in the size of one or more lesions, or the occurrence of new lesions during the course of treatment.

In cases where the patient could not be classified within CR, PR or PD categories, the response was categorised as stable disease.

Follow-up was calculated according to Shuster recommendation [28] using a median time to censoring derived from a reverse Kaplan–Meier analysis in which the outcomes dead and censored are exchanged as recommended by Altman *et al.* [29].

Survival and response duration were computed according to consensus guidelines [30].

Table 2
Dose modifications in the event of haematological toxicity

Granulocyte count ($\times 10^9$/l)		Platelet count ($\times 10^9$/l)	Dose modification factor			
			F	C	V	P
>2.5	and	>100	1	1	1	1
1.5–2.5	and	>100	0.75	0.75	1	1
1.0–1.5	and/or	50–100	0.5	0.5	1	1
<1.0	and/or	<50	0	0	1	1

Table 3
Dose modifications in the event of non-haematological toxicity

	Dose modification factor			
	F	C	V	P
Non-Haematological[a]				
Grade 1	1	–	–	–
Grade 2	0.75	–	–	–
Grade 3	0.5	–	–	–
Grade 4	0	–	–	–
Non-haematological (peripheral neuropathy)				
Grade 2	–	–	0.5[b]	–
Grade 3 or 4	–	–	0[b]	–
Non-haematological (constipation)				
Grade 3	–	–	0.5[b]	–

[a] Nausea/vomiting, diarrhoea, hair loss and haemorrhage were excluded from this rule.
[b] Until end of study.

3. Results

Patient characteristics are shown in Table 4. All patients had stage III–IV disease, and all were over 60

Table 4
Patient characteristics ($n = 23$)

Characteristic	*n* (%)
Median age, years (range)	68 (61–76)
Stage IV	17 (74)
Performance status ⩾2	2 (9)
Elevated LDH	3 (13)
Nodal sites >4	8 (35)
Haemoglobin level <120 g/l	10 (43)
Bone marrow involvement	14 (61)
Creatinine clearance ml/min	
>90	3 (13)
70–90	5 (22)
50–70	13 (56)
30–50	2 (9)
Histology	
Follicular lymphoma	10 (43)
Mantle cell lymphoma	8 (35)
Small lymphocytic lymphoma	3 (13)
MALT type	1 (4.5)
Unspecified low-grade lymphoma	1 (4.5)
FLIPI	
0, 1	0
2	7 (30)
3–5	16 (70)
Bulky masses ⩾5 cm	9 (43)
B-symptoms (>10% weight loss)	2 (9)

Abbreviation: MALT, mucosa-associated lymphoid tissue.

years of age (median 68 [range 61–76] years). Thirteen patients were female and 10 were male. The majority of patients (70%) had an Follicular Lymphoma International Prognostic Index (FLIPI) score of 3–5 (high-risk group), while the remaining patients (30%) had an FLIPI score of 2 (assessed using disease stage, lactate dehydrogenase [LDH] level, age, number of nodal sites and haemoglobin level) [31].

3.1. Safety (assessed according to WHO criteria)

Dose reductions by cycle are shown in Table 5. Few reductions were required at Dose levels 1, 2A and 2B. After seven patients had been treated at Dose level 3, an increasing number of dose reductions were required, predominantly after Cycle 4, and two opportunistic infections occurred, as well as three episodes of grade 3–4 infections. Therefore, four additional patients were treated at Dose level 2A. Grade 3 and 4 haematological adverse events were rare in the first three cycles, but became increasingly common after Cycle 4, particularly at Dose level 3 (Table 6). Haematological and non-hematological adverse events according to the number of cycles are shown in Table 7. The most apparent cumulative toxicity in the patient population overall was grade 3 or 4 neutropenia. There were no significant differences in terms of infection rates (grades 3–4), opportunistic infections (OIs) and thrombocytopenia (grades 3–4) but the number of events was insufficient to detect any trend. One patient at Dose level 2B experienced grade 4 thrombocytopenia that persisted into follow-up, reverting to normal 1 year after the end of treatment.

A greater incidence of adverse events was observed in patients with poor creatinine clearance. In patients with creatinine clearance levels $\geqslant 70$ ml/min, the incidences of unacceptable toxicities and grade 3–4 neutropenia were significantly reduced, compared with those with creatinine clearance levels of <70 ml/min (7% *vs.* 24% of cycles, $P = 0.018$; 19% *vs.* 41%, $P = 0.012$, respectively). There were no significant differences for grade 3–4 thrombocytopenia, infection rates and OIs (2% *vs.* 3%, 2% *vs.* 6% and 0% *vs.* 3%, respectively).

Two patients at Dose level 3 experienced OIs after eight cycles of treatment. The first patient developed buccal and oesophageal mucositis, and lost 4 kg in weight, due to difficulty in eating. This patient is currently alive with signs of disease progression. The second patient developed grade 4 intercerebral toxoplasmosis during follow-up, and died from another intercurrent disease.

An additional patient at Dose level 3 developed multiple infectious complications during the first cycle of treatment. This patient experienced grade 4 toxicity in the form of septic shock, and tested positive for *Klebsiella*, *Proteus mirabilis* (septicaemia) and *Escherichia coli* (uraemia); this toxicity was resolved by antibiotics.

Table 5
Dose reduction: percentage doses given by cycle

Dose level	Cycle						
	2	3	4	5	6	7	8
1	S	S	S	FC 65%	FC 65%	–	–
1	S	S	FC 65%	–	–	–	–
1	S	S	S	S	S	FC 65%	S
1	S	V 50%	S	S	S	S	S
2A	V 75%	V 50%	FC 50% V 66%	F 40% V 0%	FV 0% C 75%	–	–
2A	S	S	S	S	S	S	S
2A	S	S	S	S	S	FC 50%	FC 50%
2A	S	S	S	S	S	S	S
2B	S	S	S	S	S	S	FC 0%
2B	S	S	S	FC 65%	–	–	–
2B	FC 75%	S	S	S	S	S	FC 0% V 50%
3	S	S	S	S	F 65%	FC 65%	FC 65%
3	S	S	S	FC 75%	FC 75%	FCV 75%	V 75%
3	FC 50% V 75%	FC 50% V 75%	FC 50% V 75%	FCV 75%	FC 33% V 75%	S	FC 0%
3	V 50%	V 50%	V 50%	FC 0% V 50%	V 50%	FC 50%	FC 50%
3	S	S	S	FC 75%	S	S	S
3	S	F 0%	F 0%	F 0%	F 0%	F 0%	F 0%
3	FC 70%	C 70%	FC 75%	–	–	–	–
2A	S	FC 75%	FC 0%	FC 50%	FC 50% V 75%	F 0% C 50% V 75%	F 0% C 50% V 75%
2A	FC 50%	F 75% C 50%	F 75% C 50%	F 75% C 50%	F 75% C 50%	FC 75%	FC 75%
2A	S	S	S	S	FC 75%	FC 50%	FC 50%
2A	S	S	S	FC 75%	FC 0%	FC 50%	FC 0%

Abbreviations: F, fludarabine phosphate; C, cyclophosphamide; V, vincristine; S, standard dose (100% F, 100% C, 100% V).

Table 6
Haematological adverse events (per cycle and patient) and non-haematological adverse events (per patient)

	n (%)			
Haematological adverse events	Dose level 1	Dose level 2A	Dose level 2B	Dose level 3
Number of cycles	26	62	29	52
Neutropenia grade 3–4	6 (24)	11 (18)	8 (28)	9 (17)
Febrile neutropenia	0	0	0	0
Infection grade 3–4	0	1 (2)	1 (3.5)	2 (4)
Opportunistic infections	0	0	0	2 (4)
Thrombocytopenia grade 3–4	0	1 (2)	3 (10.5)	0
All grades 3–4	10 (38)	27 (44)	7 (11)	14 (27)
Patients	4	8	4	7
Neutropenia grade 3–4	3/4 (75)	7/8 (87.5)	3/4 (75)	5/7 (71)
Infection grade 3–4	0	1/8 (12.5)	1/4 (25)	2/7 (28.5)
Thrombocytopenia grade 3–4	0	1/8 (12.5)	3/4 (75)	0
Non-haematological adverse events				
Opportunistic infections	0	0	0	2/7 (28.5) mucositis
Cerebral toxicity	0	0	0	1/7 (14)

Table 7
Haematological and non-haematological adverse events according to number of cycles

	n (%)		
	Cycle 1–4	Cycle 5–8	*P*-value
Number of cycles	92	77	
Neutropenia grade 3–4	11 (12)	25 (32.5)	0.0014
Infection grade 3–4	3 (3)	3 (4)	ns
Opportunistic infections	0	2 (2.5)	ns
Thrombocytopenia grade 3–4	0	4 (5)	ns

Abbreviation: ns, not significant.

3.2. Efficacy

At the end of treatment, the ORR was 78% (65% CR). Outline of responses according to number of cycles and to dose levels are outlined in Table 8. The majority of responses occurred after four cycles of treatment. Seven patients who achieved CR (three at Dose level 2A, two at Dose level 2B, two at Dose level 3) subsequently relapsed at 11, 13, 15, 25, 30, 35 and 36 months, respectively. Among ten patients with follicular lymphoma, seven achieved CR and three failed to respond to F–CVP. Seven of eight mantle cell lymphomas responded to treatment, including six CRs. All three lymphocytic lymphomas responded to treatment (one CR).

At a median follow-up of 68.8 (range: 58.1–79.5) months, eight patients died from disease progression; three died from intercurrent disease; four are alive with signs of disease progression; one is alive with another cancer (ovarian cancer); and seven remain alive and free of disease. Median overall survival was 70.3 months (Fig. 1) and 3-year survival was 65% (±10%). Of the

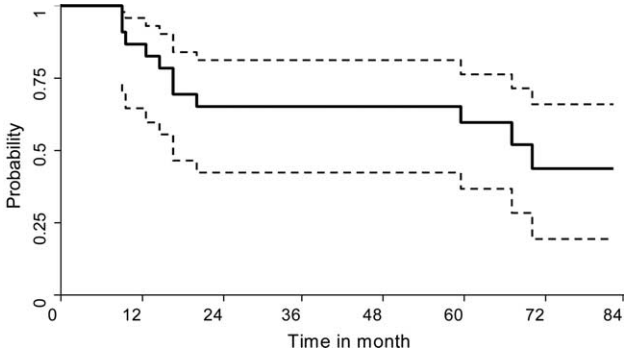

Fig. 1. Overall survival (23 patients).

Table 8
Treatment response by cycle and dose level

	n (%)			
	Post-cycle 2	Post-cycle 4	Post-cycle 6	Post-cycle 8
CR	5 (22)	13 (56)	12 (52)	15 (65)
PR	18 (78)	8 (35)	7 (31)	3 (13)
Progression	–	2 (9)	4 (17)	5 (22)
	Dose level 1	Dose level 2A	Dose level 2B	Dose level 3
CR	2	7	3	4
PR				2
Progression	2	1	1	1

Total number of patients = 23.

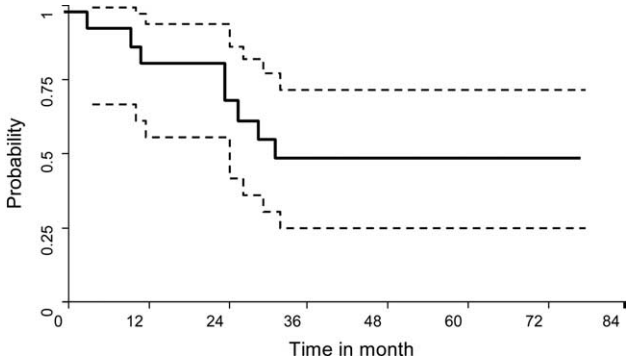

Fig. 2. Response duration (18 patients).

patients who died, two were treated at Dose level 1, three at Dose level 2A, two at Dose level 2B and four at Dose level 3 (including three deaths from intercurrent disease).

Among 18 responders, 51% were still in response at 3 and 5 years. Median response duration was not reached at the time of the analysis (Fig. 2).

4. Discussion

This dose-finding study in elderly patients has established Dose level 2A (25 mg/m^2 fludarabine phosphate, 40 mg/m^2 prednisone, Days 1–5; 500 mg/m^2 cyclophosphamide, 1 mg/m^2 vincristine, Day 1) as the maximum tolerated dose of F–CVP.

Although the design of the trial allowed for recruitment to be returned to lower dose levels in the event of more than two patients experiencing grade 3 or 4 adverse events, this did not occur at Dose levels 1, 2A and 2B, and recruitment proceeded smoothly to the highest dose level. Late toxicities at Dose level 3, in which the doses are equal to those given when fludarabine phosphate and CVP are used separately, led to a return to recruitment at Dose level 2A. The dose-limiting toxicities at Dose level 3 were neutropenia and infections; neutropenia was also more common during Cycles 4–8 of Dose level 2B, compared with 2A.

Predictors of adverse events were renal function (unacceptable toxicities and grade 3–4 neutropenia), dose level (unacceptable toxicities) and number of cycles given (grade 3–4 neutropenia). Since most adverse events occurred during later cycles, and responses were attained during earlier cycles, a reduction of the duration of treatment from eight to 4–6 cycles may be advisable.

All the dose levels assessed were highly effective, and many of the responses were durable, with a large proportion of patients alive and free of disease after intervals of up to 4.5 years. The combination therapy was highly effective in clearing disease in patients with nodal and bone marrow involvement.

These results confirm the high efficacy of fludarabine phosphate-based combination chemotherapy in untreated patients with NHL. Fludarabine phosphate plus cyclophosphamide is currently under active investigation as first-line and salvage therapy, either alone [32,33] or with the addition of mitoxantrone [34]. The convenience of these combination regimens may be further enhanced by the recent availability of an oral formulation of fludarabine phosphate, with equivalent efficacy to iv fludarabine phosphate, which can be used both as single therapy [35–37] and in combination with cyclophosphamide [32]. Furthermore, considering recent results, activity of these combinations can probably be enhanced without increasing too much the risk of toxicity by the addition of rituximab [38]. Considering all the results together, fludarabine-based combinations can probably be proposed either frontline to patients with adverse prognostic features or for relapsing/refractory disease as a second- or third-line treatment. Shortening of treatment duration will probably decrease toxicity and lead, considering the high efficacy observed, to propose it more widely as a front-line treatment of small B-cell lymphomas.

To date, few studies have focused on elderly patients. Here, we have established that an appropriate regimen of F–CVP is both effective and well tolerated in such patients. Additional large-scale studies are warranted to determine the efficacy of F–CVP, possibly with addition of rituximab, in this setting to determine whether this kind of combination can be suitable to treat low-grade B-cell lymphomas efficiently and safely in the elderly as compared to other combinations such as R-CVP [39] and R-CHOP [40].

Conflict of interest statement

None declared.

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