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*Short communication*

# Phase II study of a new alkylating agent (PTT-119) in resistant-relapsed non-Hodgkin's lymphomas*

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**Summary.** In a phase II study we evaluated the effect and toxicity of a new alkylating agent, PTT-119, in 26 patients with non-Hodgkin's lymphomas (NHL) resistant to or relapsed after other chemotherapy. PTT was scheduled by escalating the dose from 2.0 to 3.3 mg/kg every 3 weeks. Among 21 evaluable patients with NHL, 12 (57%) showed a good response (CR + PR) to PTT-119. Tolerance was acceptably good; no major side effects related to liver, cardiac, or renal toxicity were recorded. The most commonly recorded side effects were nausea and vomiting, alopecia, and phlebitis; diarrhea and drug-related fever were rarely seen. This report indicates a potential usefulness for PTT-119, a non-cross-resistant alkylating agent, in the treatment of NHL.

## Introduction

3-(*p*-Fluorophenil)-L-alanyl-3-*m-bis*(2-chloroethyl)-aminophenyle-L-alanyl-L-methionine-ethyl ester hydrochloride (PTT-119) is a tripeptide carrying an alkylating moiety [2], which has been demonstrated in experimental models using animal and human cell lines to be non-cross-resistant with other alkylating agents [8].

After the completion of a previous phase I study on solid tumors [4], we initiated a phase II study to evaluate the effect of PTT-119 on non-Hodgkin's lymphomas (NHL). The results indicate that PTT-119 was effective against NHL, with acceptable toxicity.

## Patients and methods

Patients were entered in the study according to the following criteria: (1) a diagnosis of non-Hodgkin's lymphoma (NHL) of any histological type; (2) patients with disease resistant to or relapsed after other therapy, including combination or single-agent chemotherapy currently considered to be effective; (3) a minimal interval of 4 weeks since previous therapy; (4) easily detectable disease at the time of entry into the study; (5) a performance status of $<3$, with the patients' informed consent; (6) normal hepatic, cardiac, and renal function.

PTT-119 was kindly provided by Proter-Spa (Milan) in vials containing 36 mg powder. The first dose was 2.0 mg/kg given in a 45- to 60-min infusion in 250 ml sterile saline. Subsequent doses were given every 3 weeks, escalating to 3.3 mg/kg, using the above described modalities. A minimum of three doses were scheduled except where a clear progression of disease was documented.

A total of 26 patients entered the study, including 17 men and 9 women; the mean age was 60.5 years (range, 21–82). According to the working formulation, 14 patients had high-grade, 5, intermediate-grade, and 7, low-grade malignancy. All patients had disseminated disease (stages III-IV). Previous therapy consisted of CVP [6], CHOP [5], BACOP [7], Pro-Mace-MOPP [3], and/or Chlorambucil.

A complete remission (CR) was considered to have occurred when a disappearance of masses was documented. A partial remission (PR) was defined as a reduction of $>50\%$ in masses, and no response (NR), as either no change or progressive disease. Clinical toxicity was evaluated every 3 weeks by hepatic, cardiac, and renal function tests. Hematologic toxicity was evaluated at weekly intervals, taking into account drug-related neutropenia and thrombocytopenia as well as clinical manifestations due to cytopenia.

## Results

The patients' response to PTT-119 treatment is summarized in Table 1. Among 21 evaluable patients with NHL, 12 (57%) showed a good response (CR + PR). The best response was recorded in high-grade malignancy lymphomas (70%).

The 21 evaluable patients received a total of 68 cycles of PTT-119 (mean, 3.1; range 1–8). Consistent responses (CR + PR) were recorded, regardless of previous therapy. At the time of this writing, the mean duration of response is 8+ months (range, 3–14+), and nine patients are still free of progressive disease.

In all, 24 patients were evaluable for clinical toxicity and tolerance. Side effects were nausea and vomiting (30.7%), alopecia (43.5%), and superficial phlebitis due to drug infusion (17.9%). These problems, especially nausea and vomiting, were correlated to the dose. A progression in the number of side effects was observed with increases in the dose from 2.7 to 3.3 mg/kg (data not shown). Phlebitis occurred only when the drug was diluted in 250 ml sterile saline; however, this problem was minimized by diluting PTT-119 in 500 ml solution.

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**Table 1.** Clinical features of 21 patients with NHL treated with PTT-119 and their response to the drug

| Initials | Sex | Age | Diagnosis | Date diagnosis | Previous therapy (number of cycles) | Status of disease at start of PTT-119 | Doses of PTT-119 | Response | Duration of response (months) |
|---|---|---|---|---|---|---|---|---|---|
| A.B. | M | 37 | HG | 5/86 | Pro-Mace-MOPP (3) | Refractory disease | 8 | PR | 8+ |
| G.P. | F | 71 | HG | 8/86 | CHOP (3) | Refractory disease | 7 | PR | 8+ |
| R.M. | F | 52 | HG | 7/85 | BACOP (8) | Resistant relapse | 4 | PR | 5 |
| G.F. | M | 66 | HG | 4/86 | CHOP (3), CVP (6) | Refractory disease | 3 | PR | 7+ |
| G.L. | F | 82 | HG | 6/86 | CVP (6) | Refractory disease | 3 | PR | 6+ |
| G.Z. | M | 72 | HG | 9/86 | CVP (3) | Refractory disease | 3 | PR | 6 |
| G.L. | M | 75 | HG | 4/86 | CHOP (6) | Refractory disease | 3 | PR | 9+ |
| V.K. | M | 36 | HG | 7/82 | CHOP (5), CVP (8) | Resistant relapse | 2 | NR | – |
| M.B. | M | 74 | HG | 7/85 | BACOP (6) | Resistant relapse | 1 | NR | – |
| G.S. | M | 51 | HG | 6/86 | BACOP (10) | Resistant relapse | 3 | NR | – |
| E.N. | M | 56 | IG | 1/86 | CHOP (2), CVP (8) | Resistant relapse | 3 | PR | 4 |
| U.F. | M | 64 | IG | 4/86 | BACOP (6) | Resistant relapse | 3 | PR | 8+ |
| O.V. | F | 43 | IG | 10/80 | CHOP (4), CVP (6) | Resistant relapse | 3 | MR | 5 |
| D.P. | M | 72 | IG | 10/86 | CVP (5), BACOP (4) | Refractory disease | 3 | MR | 3 |
| M.P. | F | 48 | LG | 12/82 | CVP (6) | Resistant relapse | 3 | CR | 14+ |
| D.B. | M | 72 | LG | 3/83 | CVP (8) | Refractory disease | 7 | PR | 13+ |
| D.N. | M | 60 | LG | 5/83 | Chlorambucil | Refractory disease | 3 | PR | 14+ |
| B.B. | M | 62 | LG | 2/85 | CVP (6), α-IFN | Refractory disease | 2 | NR | – |
| A.B. | F | 53 | LG | 4/86 | CVP (3) | Refractory disease | 1 | NR | – |
| F.M. | M | 43 | LG | 12/78 | CVP (4), BACOP (6) | Refractory disease | 2 | NR | – |
| P.P. | F | 61 | LG | 12/86 | Chlorambucil | Refractory disease | 2 | NR | – |

HG, high-grade malignant lymphoma; IG, intermediate-grade malignant lymphoma; LG, low-grade malignant lymphoma; CR, complete remission; PR, partial remission; MR, minor response; NR, no response

No complications related to renal, hepatic, or cardiac toxicity were recorded. Hematologic toxicity (Table 2) was quite different according to the type of presentation. The group of patients without bone marrow involvement (8 patients) showed a mean nadir of $2.8 \times 10^3/\mu l$, $204 \times 10^3/\mu l$, and 12.4 g/100 ml for polymorphonuclear neutrophilic leukocytes (PMNs) platelets (PLTs), and hemoglobin, respectively. Two cases (25%) showed mild myelosuppression (PMN $< 1.5 \times 10^3/\mu l$). Among a total of 27 doses of PTT-119, therapy was delayed three times; in these cases, hematologic recovery was detected within 1 week.

In 12 patients with bone marrow involvement but normal PMN, PLT, and hemoglobin values before PTT-119, a sensible reduction of these parameters was observed (Table 2). Eight patients showed myelotoxicity and 8 of 24 drug doses were delayed; hematologic recovery occurred within 1–3 weeks. Three major episodes of infection were documented. Although no deaths related to cytopenia were recorded, one definitive interruption of drug delivery was necessary due to persistent thrombocytopenia.

The last group of four patients with bone marrow disease and impairment of blood parameters showed the worst hematologic tolerance. Despite a reduction in dose, all patients showed a further decrease in hematologic values, indicating myelosuppression. Of 17 total doses of PTT-119, 8 were delayed, and three patients underwent definitive interruptions of treatment. However, no deaths related to hematologic toxicity were recorded.

## Discussion

A number of experimental models using cell lines resistant to other alkylating agents, such as melphalan, have demonstrated the great difficulty of inducing resistance to

**Table 2.** Hematological toxicity and clinically related complications expressed by the number of protocol violations and major side effects

| | Patients with normal bone marrow | Patients with bone marrow involvement and normal blood values | Patients with bone marrow involvement and decreased blood parameters |
|---|---|---|---|
| Total number of patients | 8 | 12 | 4 |
| Mean nadirs after first cycle: | | | |
| Neutrophils | $2.8 \times 10$/dl | $2.3 \times 10$/dl | $1.7 \times 10/\mu l$ |
| Platelets | $204 \times 10$/dl | $128 \times 10$/dl | $95 \times 10$/dl |
| Hemoglobin | 12.4 g/dl | 10.9 g/dl | 8.8 g/dl |
| Myelotoxicity/patients | 2/8 (25%) | 10/17 (59%) | 14/14 (100%) |
| Number of delayed cycles | 3/27 (11%) | 8/24 (33%) | 8/17 (48%) |
| Number of definitive interruptions/patients | 0 | 1/12 (8%) | 3/4 (75%) |
| Hematologic recovery (weeks) | 1 | 1–3 | – |
| Number of infections/patients | 0 | 3/12 (25%) | 2/4 (50%) |

PTT-119 [9]. The main hypothesis is that PTT-119 is a bifunctional alkylating compound in which the combination of three peptides in the L-configuration alters and/or increases the transport of the alkylating moiety in the drug across the tumor cell membrane. This difference in the degree of transport into the cell could produce the increased cytolitic activity of PTT-119 compared with similar drugs [9]. Many NHLs show progression due to the emergence of clones resistant to the drugs commonly used. The basic strategy is to prevent such resistance by the use of a wide range of different drugs given in the best possible combination. Although this approach is widely used in the treatment of disseminated NHL, resistance occurs quite frequently, specially in cases showing a slow response rate.

Our preliminary experience in NHL seems to demonstrate the influence of resistance to previous therapy on the response to PTT-119. This result seems to reproduce in vivo what has been demonstrated in vitro by using the L1210 cell line [1]. Thus, PTT-119 appears to be indicated as a non-cross-resistant agent in combination therapy for the prevention of relapse.

One important limiting factor in using PTT-119 is hematologic toxicity. However, although this problem has often been recorded, hematologic toxicity was almost always observed only in patients with low hematologic tolerance due to bone marrow involvement or previous therapy. We suggest that this problem could be avoided or minimized in earlier phases of disease.

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