

Mitoxantrone, prednisone, pentostatin and bleomycin for patients with indolent non-Hodgkin's lymphoma relapsed or unresponsive to previous treatments. Results of a phase II study conducted by the *Gruppo Italiano per lo Studio dei Linfomi (GISL)*

Research Article

Massimo Federico^{1*}, Vincenzo Callea², Romano Danesi³, Antonella Montanini¹, Nicola Di Renzo⁴, Mario Petrini³, Mario Del Tacca³, Maria Angela Sirotti¹, Giovanni Santacrose¹, Alberto Bagnulo¹, Matteo Dell'Olio⁵ and Maura Brugiattelli⁶ for GISL

¹Dipartimento di Oncologia ed Ematologia, Università di Modena e Reggio Emilia; ²Divisione di Ematologia, Presidio Ospedali Riuniti "Bianchi, Melacrino, Morelli", Reggio Calabria; ³Divisione di Farmacologia e Chemioterapia, Dipartimento di Oncologia, Trapianti e Tecnologie Avanzate in Medicina, Università di Pisa; ⁴Unità Operativa di Ematologia ed Oncologia Medica, C.R.O.B., Ospedale Oncologico Regionale, Rionero in Vulture (PZ); ⁵Divisione di Ematologia, Centro Trapianti di Midollo Osseo, IRCCS "Casa Sollievo della Sofferenza", S. Giovanni Rotondo (FG); ⁶Divisione di Ematologia, Azienda Ospedaliera Papardo, Messina.

*Correspondence to: Massimo Federico, Dipartimento di Oncologia ed Ematologia, Centro Oncologico Modenese, Università di Modena e Reggio Emilia, Policlinico - Via del Pozzo 71, 41100 Modena, Italy. Phone +39-059-4224547; Fax +39-059-4224549; e-mail: federico@unimore.it

Key words: chemotherapy, indolent NHL, MiPPeB, non-Hodgkin's lymphoma, Pentostatin

Received: 25 March 2003; Accepted: 10 April 2003; electronically published: April 2003
Contributed by Massimo Federico

Summary

Background. Taking into account the promising results achieved with purine analogs in combination regimens in patients with indolent NHL, we designed a phase II study aimed at assessing the efficacy of Pentostatin in combination with Mitoxantrone, Prednisone and Bleomycin (MiPPeB). **Patients and Methods.** Thirty patients (18 males and 12 females) with relapsed or unresponsive indolent NHL were treated with MiPPeB. The treatment consisted of Pentostatin 5 mg/m², on day 1 and 8, Mitoxantrone 10 mg/m², on day 1, Bleomycin 8 mg/m², on day 8, Prednisone 100 mg, on day 1 and 8; cycles were administered at 3 week intervals for a maximum of 6 cycles. In 5 patients we investigated the pharmacokinetics of Pentostatin and 2'-deoxyadenosine. **Results.** A median of 5 cycles (range 2-6) was administered. Ten Complete Remissions (CRs) and 8 Partial Remissions (PRs) were observed, with an overall (CR+PR) response rate of 60%. The median response duration was 38 months (95% CI: 28 to 48 months). The actuarial 3-year relapse free survival for 10 patients in CR was 57%. The 3-year overall and failure free survival rates were 71% and 23%, respectively. Toxicity was mainly hematological with grade 3-4 neutropenia in 37% and grade 3 thrombocytopenia in 7% of the cases. **Conclusion.** MiPPeB, as used in the present study, showed a promising activity with acceptable toxicity in patients with relapsed or unresponsive indolent NHL and resulted in durable remission.

I. Introduction

Low-grade non-Hodgkin's lymphomas (NHL) or, as they are now defined, indolent NHL (Harris et al, 1994;

Harris et al, 2000), include different disease entities characterized by a similar clinical course, with a relatively long median survival and, usually, good response to initial therapy. A typical feature in the clinical course of patients

with indolent NHL is their tendency to relapse, with subsequent responses of progressively shorter duration (Horning, 1993). New therapeutic approaches for indolent NHL currently under investigation include (a) attempts to eradicate the disease using high-dose chemotherapy with stem cell rescue (Schouten et al, 1994; Ladetto et al, 2002) and (b) new combinations of drugs of known specific efficacy in these diseases.

Fludarabine (2-fluoro-ara-AMP), 2-CdA (2-chlorodeoxyadenosine) and Pentostatin (2-deoxycoformycin) are new structurally similar purine nucleoside analogs (**Figure 1**) recently considered with increasing interest for the treatment of different lymphoproliferative disorders, including hairy cell leukemia (Chassileth et al, 1991; Ganeshaguru et al, 1991), chronic lymphocytic leukemia (Bergmann et al, 1993; Keating et al, 1998;), cutaneous T-cell lymphomas (Grever et al, 1983; Foss et al, 1994), and indolent NHL (Hoffman et al, 1994). The sensitivity of indolent NHL to purine analogs is now largely demonstrated, although the majority of studies deal with Fludarabine (Hochster et al, 1992; Redman et al, 1992) and 2-chlorodeoxyadenosine (Brugiattelli et al, 1996; Robak et al, 2001).

So far, Pentostatin has been less commonly employed for the treatment of NHL (Cummings et al, 1991; Iannitto et al, 2002), although its efficacy has been well documented in other indolent lymphoproliferative disorders such as hairy cell leukemia (Grever et al, 1995), prolymphocytic leukemia (Dohner et al, 1993), Sezary Syndrome and Mycosis Fungoides (Mercieca et al, 1994). More recently a higher activity of purine analogs has been demonstrated in combination regimens (McLaughlin et al, 1994; Tobinai et al, 1995; McLaughlin et al, 1996; Flinn et al, 2000).

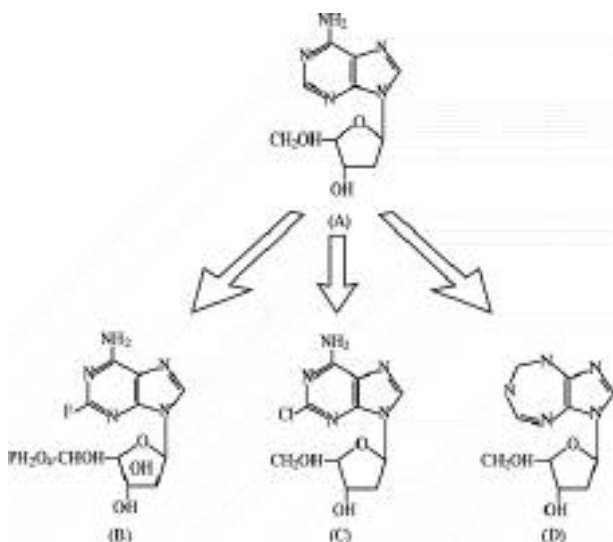


Figure 1: The structures of deoxyadenosine (A), and the purine analogs fludarabine (B), 2-chlorodeoxyadenosine (C), and 2'-deoxycoformycin (D).

Considering that in patients with indolent NHL the highest therapeutic activity of purine analogs was obtained in combination regimens and, in particular, the promising results of the combination with Mitoxantrone and steroids, we designed a phase II pilot study aimed at assessing the efficacy of Pentostatin in combination with Mitoxantrone, Prednisone and Bleomycin (MiPPeB) in patients with relapsed or unresponsive indolent NHL. Bleomycin was added to the schedule in order to increase the absolute dose intensity of the regimen since this drug is characterized by very limited myelotoxicity that favors its use in combination regimens. Moreover, considering that (a) the pharmacokinetic of Pentostatin is not well described in the literature, (b) limited data are available concerning the pharmacodynamic effect of the drug, and (c) information on drug distribution would be helpful in optimizing its use in combination regimens, in 5 patients we also investigated the pharmacokinetics and pharmacodynamic effect of Pentostatin.

II. Patients and methods

Between November 1997 and July 2000, 30 patients with indolent NHL, were registered for the study and scheduled to receive 6 courses of a combination of Mitoxantrone, Prednisone, Pentostatin and Bleomycin (MiPPeB). The characteristics of these patients are summarized in **Table 1**. Patients were eligible for the study if they presented with a diagnosis of indolent NHL (categories A-D of the Working Formulation, or lymphocytic or follicular lymphoma of the R.E.A.L. classification), had relapsed or were unresponsive to previous therapy and presented with active disease. According to the Gruppo Italiano per lo Studio dei Linfomi (GISL) criteria (Morabito et al, 2002), active phase of the disease was defined as the presence of at least one of the following signs or symptoms: presence of systemic symptoms; bulky disease (>5 cm); anemia (Hb <10 g/L) or thrombocytopenia (Plt <100.000/L); diffuse bone marrow pattern of infiltration; lymphocyte doubling time (LDT) <12 months or a doubling of the maximum diameter of at least 3 measurable sites in less than 12 months.

Patients unresponsive to previous therapy could be included only in case of no treatment requirement for the last 6 months. Additional inclusion criteria were: age 18-75 years; stage II-IV; no more than 3 previous lines of chemotherapy; life expectancy >6 months; absence of history of repeated and/or severe infectious complications; absence of cardiac, renal, hepatic and respiratory failure; ECOG performance status 0-2; HBsAg negativity, HCV-RNA negative in HCV-Ab positive cases.

Exclusion criteria included: severe or symptomatic restrictive or obstructive lung disease; ejection fraction less than 50%, signs or symptoms of congestive heart failure, or myocardial infarction within the past 3 months, angina pectoris, any major ventricular arrhythmia, or uncontrolled blood pressure; active infections; concurrent or previous malignancy, other than non melanomatous skin cancer, surgically cured carcinoma in situ of the cervix, or a history of cancer that had not been active in the past 5 years; patients who were HIV positive or who had AIDS or ARC.

The present protocol was approved by the ethical committees according to the local rules and the period. It was the responsibility of the investigator to ensure that each patient gave her/his consent in writing, prior to participating in this study. All completed informed consent forms were retained by the investigator.

Table 1. Patient characteristics.

Characteristics	No.	%
Sex		
Male	18	60
Female	12	40
Age		
60 years	18	60
>60 years	12	40
WHO performance status		
0	21	70
1	8	27
2	1	3
IPI		
0 - 1	15	50
2	12	40
Not assessable	3	10
Systemic symptoms		
Absent	22	73
Present	8	27
Bulky disease		
No	27	90
Yes	3	10
Leukemic Phase		
No	26	33
Yes	4	13
Beta2-microglobulin levels		
High	10	33
Normal	16	54
Not assessed	4	13
Doubling time		
>12 months	17	57
<12 months	7	23
Not assessable	6	20
Previous therapy		
1	9	31
2	10	33
3	11	36

A. Treatment plan

Patients received a maximum of 6 courses of the MiPPeB regimen, given every 3 weeks, in an outpatient setting according to the following schedule: Pentostatin 5 mg/m², on days 1 and 8, at hour 0, administered as an IV infusion in 100 ml of normal saline, over 30 minutes; Prednisone 100 mg, on days 1 and 8, at hour 0, administered as an IV infusion in 50 ml of normal saline, over 15 minutes; Mitoxantrone 10 mg/m², on day 1, at hour 6, administered as an IV infusion in 100 ml of normal saline, over 30 minutes; Bleomycin 8 mg/m², on day 8, at hour 4, administered as an IV infusion in 100 ml of normal saline, over 15 minutes (**Figure 2**).

The MiPPeB courses were given at 21-day intervals, provided that at the time of recycling WBC count was >4.0 x 10⁹/L, and platelet count >100 x 10⁹/L. If the above-mentioned criteria were not satisfied on the day of recycling, the administration of a subsequent MiPPeB course was performed according to the dose modifications rules reported in **Table 2**.

B. Response assessment

Response to treatment was assessed within four weeks after the end of the last chemotherapy. At this time, a CT-scan of the chest and abdomen/pelvis was performed together with any other instrumental investigation found to be abnormal at any previous evaluation. Complete remission (CR) was defined as the disappearance of all clinical evidence of disease and the normalization of all laboratory values and radiographs abnormal before starting treatment. Patients who achieved CR during therapy, but relapsed within 30 days after therapy had been completed, were classified as non responders. Partial remission (PR) was defined as a greater than 50% reduction in the largest dimension of each anatomic site of measurable disease for at least one month. No remission (NR) was defined as a less than 50% regression or stable or progressive disease. All early deaths due to disease progression or treatment-related toxicity were considered as treatment failure, and included in the group of NR.

Patients were considered evaluable for response assessment after at least 3 courses, unless treatment was discontinued because of disease progression or early death. Toxicity was assessed according to the WHO criteria.

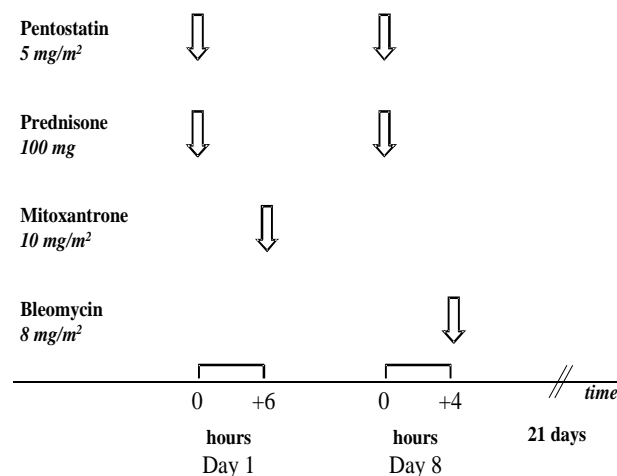


Figure 2. Treatment plan.

Table 2. Dose modifications.

WBC	PLT	DOSES	DRUGS
>4.0	>100	100%	All
3.9 - 3.0	99 - 75	100%	Bleomycin
		50%	Mitoxantrone
			Pentostatin
<3.0	<75	100%	Bleomycin
		0%	Mitoxantrone
			Pentostatin

It was the responsibility of the clinical investigators to ensure that all clinical record forms designed for the study were completed satisfactorily and returned to the trial office. The clinical investigator was required to sign each completed record form to signify that it represented an accurate record of the patient.

C. Statistical analysis

This was a prospective, open label, multicenter, phase II pilot study to assess the feasibility, safety, tolerability and efficacy of a Pentostatin-based regimen in patients with relapsed indolent NHL. The sample size was small and no statistical hypothesis testing was planned. The trial size was based on feasibility and was chosen for practical rather than statistical considerations in order to obtain information for planning a possible phase III study.

Main endpoints were: complete remission, duration of remission, disease free survival. Secondary endpoint was overall survival. All data were analyzed with the Statistical Package for the Social Sciences (SPSS), release 9.0.1. Differences in CR rates between the groups were analyzed by the Pearson's χ^2 test for contingency tables. Overall survival (OS), disease free survival (DFS) and relapse free survival (RFS) curves were estimated by the method of Kaplan-Meier. Overall survival was calculated from the beginning of treatment until death from any cause. DFS and RFS were calculated from the end of induction therapy to the first evidence of disease. Response rates, survival, relapse and toxicity were analyzed on all patients. A p value of 0.05 (two-sided) was considered the limit of significance for all the analyses.

D. Pharmacokinetic/pharmacodynamic study of Pentostatin

In addition to the clinical trial, 5 of the 30 patients were enrolled in a pharmacokinetic/pharmacodynamic study of Pentostatin.

Heparinized plasma samples were obtained at baseline (before the administration of Pentostatin) and at 5, 15, 30, 60 min, 2, 3, 6, 12, 18, 24, 48, and 72 hours after drug dose in five patients, three on day 1 and two on day 8 of treatment. Plasma concentrations of Pentostatin (Danesi et al, 2002) and 2'-deoxyadenosine (Koller et al, 1980) were assessed by specific high-performance liquid chromatography (HPLC) methods with ultraviolet detection. Intra- and inter-assay precision (coefficients of variation) were <10.1% for Pentostatin and <9.4% for 2'-deoxyadenosine. Individual plasma concentration vs. time data were fitted using non-linear least-squares regression analysis by means of computer software (MWPHARM, MediWare, Groeningen, the Netherlands) and peak plasma concentration, terminal half life, total body clearance and apparent volume of distribution at steady state were calculated by conventional methods (Rowland and Tozer, 1995).

III. Results

Between November 1997 and July 2000, 30 patients were registered for the study and all were assessable for response and toxicity.

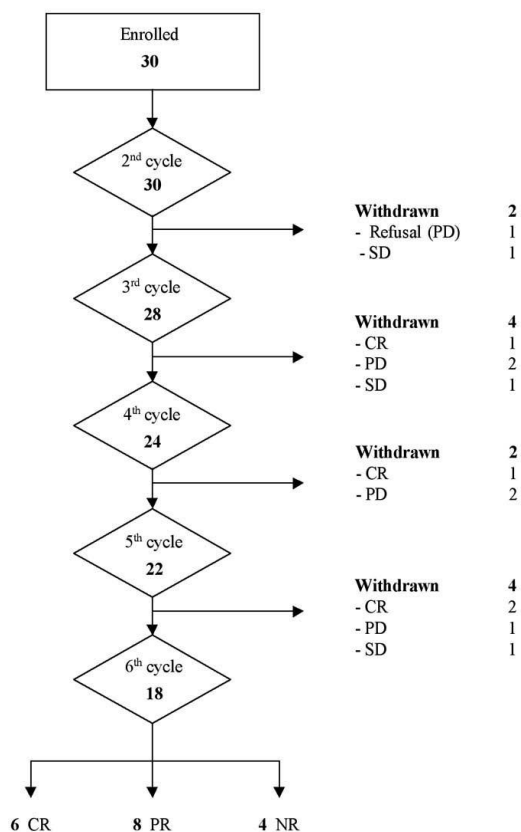
The median age was 57 years (range 36 - 72), with 18 patients younger than 60 years. Among the remaining clinical features at presentation, it should be noted that 76% had advanced (stage III or IV) disease, 13 (43%) had non follicular histology, and 5 (17%) had the involvement

of two extranodal sites. In addition, 20% presented with systemic symptoms and 23% had LDH over the normal range. Six patients were refractory to previous therapy, 12 had a duration of CR lasting less than 12 months and 12 relapsed after more than one year of CR.

At study entry 9 patients had relapsed after first line therapy, and 21 had received two or more chemotherapy regimens before MiPpEB. Seven patients had already received a purine analog (Fludarabine), in 6 cases combined with an anthracycline which in 4 of those cases, consisted of Mitoxantrone. Finally, one patient was in relapse after high dose therapy with stem cell rescue. Median time between initial diagnosis and inclusion in the present study was 46 months (range 10-110 months). The disease history lasted less than one year, 1-3 years, and more than 3 years in 6, 12 and 12 patients respectively. The mean interval between last therapy and study entry was 18 months (range 4-46 months); this interval was less than one year in 12 patients (40%), and more than one year in the remaining 18 cases. A total of 152 courses were administered to the 30 patients. The median number of cycles was 5 (range 2 to 6) and the median interval between cycles was 26 days (range 19 to 70). Twenty-eight patients completed at least 3 courses and 18 received all the 6 planned courses. Reasons for early withdrawal and status at that time are summarized in **Figure 3**. The main reason for interrupting planned therapy was progressive disease (6 patients) or unsatisfactory response (3 patients). However, four patients stopped therapy while in CR after 3, 4, 5, 5 courses, respectively, because of poor patient compliance.

A. Response

With MiPpEB, 10 patients (33%) (95% CI: 16% to 50%) achieved a CR and an additional 8 patients (27%) (95% CI: 11% to 43%) a PR, with an overall response rate of 60% (95% CI: 43% to 76%). In addition, 7 (23%) (95% CI: 8% to 39%) cases showed a durable stable phase of the disease after treatment. The objective response rate was similar for patients with early or late relapse ($p=0.247$), and for those with one or more previous therapies ($p=0.602$). After a median follow-up of 30 months (39 months for patients still alive) 6 patients out of 10 in CR relapsed. The 3-year RFS is 57% (95% CI: 27 to 52) (**Figure 4**). The median duration of remission for 18 responding patients was 38 months (range 2 - 57), better than the median duration of the last response (21 months, range 6-36 months). Nine patients died, all of them because of disease progression. The 3-year survival rate for the 30 enrolled patients is 71% (**Figure 5**). Among baseline patients' characteristics of potential prognostic value only a short doubling time was associated with a significantly lower chance of achieving a response to MiPpEB therapy ($P=0.047$). Moreover, performance status ($P=0.0192$), number of previous therapies (0.0001), and beta2-microglobulin (0.0174), resulted of prognostic relevance in univariate analysis of survival. Given the limited number of cases a multivariate analysis was not performed.



Abbreviations.
CR: Complete Remission; **PR:** Partial remission; **PD:** Progressive Disease; **SD:** Stable Disease; **NR:** No Response or Progressive Disease

Figure 3. Flow-chart of the study.

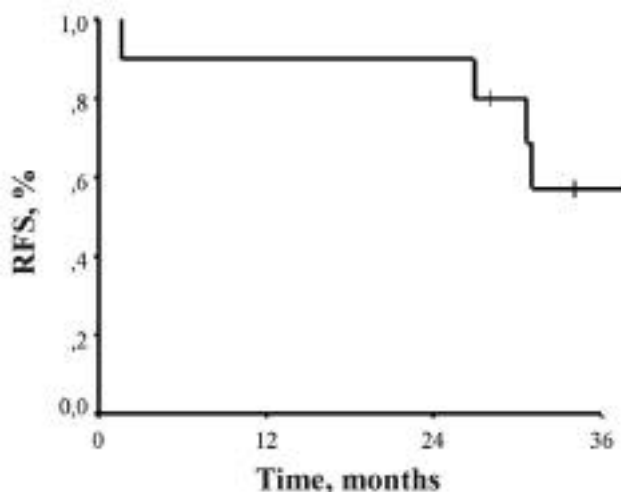


Figure 4. Kaplan Meier Relapse-free survival.

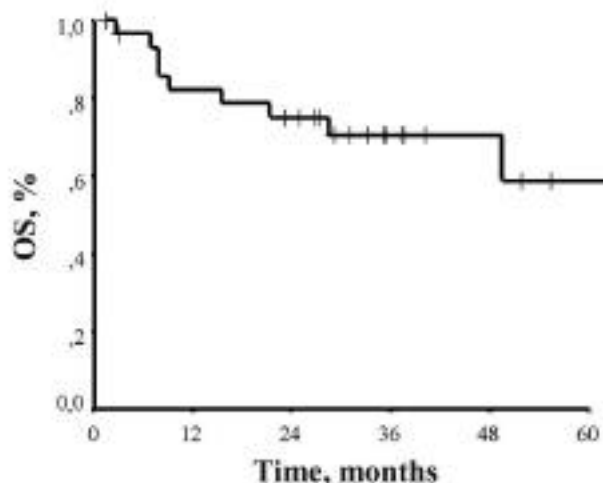


Figure 5. Kaplan Meier Overall survival.

B. Toxicity

Toxicity was rather mild, especially considering that the majority of cases were heavily pretreated. No significant organ toxicity was reported. As expected in a pretreated patient setting, toxicity was mainly hematological consisting of frequent although not severe leucopenia and in few instances thrombocytopenia. Leucopenia was not associated with severe infection occurrence.

C. Pentostatin pharmacokinetic /pharmacodynamic study

Mean peak plasma concentrations of Pentostatin and 2'-deoxyadenosine were $7 \pm 2.6 \mu\text{M}$ and $68 \pm 23 \mu\text{M}$, respectively, while mean baseline 2'-deoxyadenosine levels were $4.1 \pm 1.9 \mu\text{M}$. Plasma concentration-time curves showed a first-order elimination with biphasic decay, with a terminal half life of Pentostatin of 8.7 ± 3.1 hours. Average total body clearance (CLTB) of Pentostatin was $103.45 \pm 22.4 \text{ mL/min}$ and apparent volume of distribution at steady state (V_{dss}) was 42.4 ± 7 .

V. Discussion

One of the main features of the clinical course of indolent lymphomas is represented by its continuous pattern of relapse with subsequent responses of shorter and shorter duration after conventional chemotherapy (Hornig SJ, 1993). So far, this clinical behavior has not been changed by the introduction of purine analogs and immunotherapy with monoclonal antibodies. Some more durable responses have been reported after high dose chemotherapy with stem cell rescue (Schouten et al, 1994; Ladetto et al, 2002) although this treatment approach cannot be used in the vast majority of cases.

Therefore, keeping in mind this unavoidable tendency to relapse, it would be advisable to design a long-term treatment program for each patient by choosing among the different treatments now available for this histological category.

Therefore, the present study introduces the combination of Pentostatin with Mitoxantrone and Bleomycin among the effective therapeutic options suitable for patients with advanced indolent lymphomas.

Previously, the activity of purine analogs as single agents has been clearly demonstrated. In patients with relapsed or recurrent indolent NHL the response rate to Fludarabine ranges between 43% and 70% (Hochster et al, 1992; Hoffman et al, 1994).

Similar results have been reported for 2-CdA. In a group of 14 patients unresponsive to previous treatments, 3 CR and 4 PR have been reported by Brugiatelli et al. (1996) in a multicentric study. In a preliminary study of 26 patients with untreated indolent NHL Emanuele et al (1994) reported 35% and 54% CR and PR respectively.

As far as Pentostatin is concerned an overall response rate of 29% and 33% has been reported in patients with relapsed or refractory indolent NHL by Cummings et al (1991), and Duggan et al (1990), respectively. These two studies using Pentostatin as salvage treatment demonstrate the possibility of obtaining clinical responses, up to more than 50 months in patients with NHL.

The higher efficacy of Fludarabine in combination with Mitoxantrone as compared with its use as single agent has been repeatedly reported with response rates up to 90%, when used as first line and salvage treatment respectively (McLaughlin et al, 1994; Seymour et al, 2001). Using Fludarabine, Mitoxantrone and Dexamethasone (FND), McLaughlin et al (1996) achieved an overall response rate of 94% (47% CR and 47% PR) in a group of 51 patients with recurrent or refractory indolent NHL.

Although all purine analogs could exert similar effectiveness, so far, the clinical experience with 2-CdA and Pentostatin for the treatment of lymphomas (Cummings et al, 1991; Brugiatelli et al, 1996; Iannitto et al, 2002) is much more limited as compared to Fludarabine. At the moment their use is almost completely confined to the treatment of hairy cell leukemia (Grever et al, 1995) and in the case of Pentostatin of T-cell neoplastic diseases as a single agent (Mercieca et al, 1994). More recently, the combination of Pentostatin with Cyclophosphamide or Chlorambucil has been reported with promising results (Goodman, 2000; Waselenko et al, 2000; Weiss, 2000).

Based on the known efficacy of the combination of Fludarabine and Mitoxantrone and on in vitro data of synergism of the latter one with Pentostatin (Morabito et al, 1997), we designed the present MiPPeB schedule in order to take advantage of the synergistic effect of the two drugs, possibly potentiated by the addition of a third non-myelotoxic drug, namely Bleomycin. In addition, we tried to maximize the synergistic effect of the combination by using a time-dependent scheme of administration which could respect the biological properties of the different drugs, similar to the schedules employed for the treatment of acute leukemias.

The results of the present study performed on heavily pretreated patients show that MiPPeB combination chemotherapy induced an overall response rate of 60% with 33% CR, thus at least comparable to the results obtained with the combination of Fludarabine and Cyclophosphamide (Flinn et al, 2000) or Fludarabine and Mitoxantrone (McLaughlin et al, 1994; McLaughlin et al, 1996; Seymour et al, 2001).

The efficacy of this combination is confirmed by the duration of response which is similar that obtained in our patients by the previous treatment. It is noteworthy that out of 7 cases already treated with Fludarabine mostly in combination with Mitoxantrone 2 CR were obtained and 2 cases reached a stable disease status, thus suggesting the possibility of effectively using both purine analogs during the course of the disease.

Moreover, the toxicity profile of the MiPPeB schedule deserves a comment. The main side effect was myelotoxicity, but, despite frequent episode of neutropenia, purine analog-induced immunodepression and heavy pretreatment, often including another purine analog, infectious complications were not frequent and never severe. Only one death due to infection occurred in a patient with disease progression.

Finally, the pharmacokinetic and pharmacodynamic studies demonstrated that at the present dosing schedule, Pentostatin reaches effective ADA inhibitory levels in plasma, as shown by the increase in 2'-deoxyadenosine concentrations over baseline levels; in addition to this, the Vdss value lower than total body water indicates that extensive tissue binding does not occur, while the extent of drug clearance suggests that the kidney is the main route of drug excretion from the body, as confirmed by a recent study in patients with mild renal impairment (Lathia et al, 2002).

In conclusion, the results of the present study demonstrate the efficacy with acceptable toxicity of Pentostatin included in combination chemotherapy for the salvage treatment of indolent lymphomas not suitable for high dose chemotherapy approaches. Accordingly, MiPPeB or MiPPeB-like schedules deserve inclusion among the conventional chemotherapy options for this category of lymphoproliferative disorders and should be tested also in a front-line setting.

Acknowledgments

The study was supported by Associazione Angela Serra per la Ricerca sul Cancro, Modena, and Fondazione Ferrata-Storti, Pavia, Italy.

Participating institutions

Gruppo Italiano per lo Studio dei Linfomi (GISEL) - Chairpersons: M. Federico, P. G. Gobbi, L. Baldini.

List of Institutions contributing to the present study:

Dipartimento di Ematologia e Trasmfusionale (F. Nobile), Presidio Ospedali Riuniti "Bianchi, Melacrino, Morelli", Reggio Calabria; Cattedra e Servizio di Ematologia (A. T. Maiolo, L. Baldini), IRCCS Ospedale

Maggiore, Milano; Dipartimento di Oncologia ed Ematologia (G. Torelli, M. Federico, S. Sacchi), Università di Modena e Reggio Emilia, Modena; Divisione di Medicina (G. Partesotti, G. Santacroce), Ospedale Civile, Sassuolo, Modena; Divisione di Medicina (A. Bagnulo, A. Zoboli), Ospedale S. Sebastiano, Correggio, Reggio Emilia; Divisione di Ematologia (A.M. Carella, N. Di Renzo, M. Dell'Olio), IRCCS "Casa Sollievo della Sofferenza", S. Giovanni Rotondo, Foggia; Dipartimento di Oncologia (M. Petrini, F. Caracciolo), Divisioni di Ematologia e Farmacologia, Università di Pisa; Unità Operativa di Oncologia Medica (V. Pitini), Policlinico Universitario, Messina.

References

- Bergmann L, Fenchel K, Jahn B, Mitrou PS and Hoelzer D (1993) Immunosuppressive effects and clinical response of Fludarabine in refractory chronic lymphocytic leukemia. **Ann Oncol** 4, 371-375.
- Brugiattelli M, Holowiecka B, Dmoszynska A, Krieger O, Planinc-Peraica A, Labar B, Callea V, Morabito F, Jaksic B, Holowiecki J, Lutz D (1996) 2-Chlorodeoxyadenosine treatment in non-Hodgkin's lymphoma and B-cell chronic lymphocytic leukemia resistant to conventional chemotherapy, results of a multicentric experience. **Ann Hematol** 73, 79-84.
- Cassileth PA, Chevart B, Spiers AS, Harrington DP, Cummings FJ, Neiman RS, Bennett JM and O'Connell MJ (1991) Pentostatin induces durable remissions in hairy cell leukemia. **J Clin Oncol** 9, 243-246.
- Cummings FJ, Kim K, Neiman RS, Comis RL, Oken MM, Weitzman SA, Mann RB and O'Connell MJ (1991) Phase II trial of Pentostatin in refractory lymphomas and cutaneous T-cell disease. **J Clin Oncol** 9, 565-571.
- Danesi R, Petrini M, Loni L, Federico M, Riggi G, Del Tacca M (2002) Pharmacokinetics and pharmacodynamics of Pentostatin in non-Hodgkin lymphomas. **Proceedings ASCO** 21, 120a (abstract 479).
- Dohner H, Ho AD, Thaler J, Stryckmans P, Sonneveld P, De Witte T, Lechner K, Lauria F, Bodewadt-Radzun S and Suci S (1993) Pentostatin in prolymphocytic leukemia, phase II trial of the European Organization for Research and Treatment of Cancer, Leukemia Cooperative Study Group. **J Natl Cancer Inst** 85, 658-662.
- Duggan DB, Anderson JR, Dillman R, Case D, Gottlieb AJ (1990) 2-deoxycoformycin (Pentostatin) for refractory non-Hodgkin's lymphoma, a CALGB phase II study. **Med Pediatr Oncol** 18, 203-6.
- Emanuele S et al. (1994) 2-Chlorodeoxyadenosine (2-CDA) activity in patients with untreated low-grade lymphoma. **Proceedings ASCO** 13, 1002 (abstract).
- Flinn IW, Byrd JC, Morrison C, Jamison J, Diehl LF, Murphy T, Piantadosi S, Seifter E, Ambinder RF, Vogelsang G and Grever MR (2000) Fludarabine and Cyclophosphamide with Filgrastim support in patients with previously untreated indolent lymphoid malignancies. **Blood** 96, 71-75.
- Foss FM, Ihde DC, Linnoila IR, Fischmann AB, Schechter GP, Cotelingam JD, Steinberg SM, Ghosh BC, Stocker JL and Bastian A (1994) Phase II trial of Fludarabine phosphate and interferon alfa-2a in advanced mycosis fungoides and Sezary syndrome. **J Clin Oncol** 12, 2051-2059.
- Ganeshaguru K, de Mel WC, Sissolak G, Catovsky D, Dearden CE, Mehta AB, Hoffbrand AV (1991) Increase in 2',5'-oligoadenylate synthetase caused by deoxycoformycin in hairy cell leukaemia **Adv Exp Med Biol** 309A, 65-8.
- Goodman M (2000) Pentostatin and high dose Cyclophosphamide for the treatment of refractory autoimmune disorders. **Semin Oncol** 27 (2 suppl 5), 67-71.
- Grever M, Kopecky K, Foucar MK, Head D, Bennett JM, Hutchison RE, Corbett WE, Cassileth PA, Habermann T and Golomb H (1995) Randomized comparison of Pentostatin versus interferon alfa-2a in previously untreated patients with Hairy Cell Leukemia, an intergroup study. **J Clin Oncol** 13, 974-982.
- Grever MR, Bisaccia E, Scarborough DA, Metz EN and Neidhart JA (1983) An investigation of 2'-deoxycoformycin in the treatment of cutaneous T-cell lymphoma. **Blood** 61, 279-282.
- Harris NL, Jaffe ES, Diebold J, Flandrin G, Muller-Hermelink HK, Vardiman J (2000) Lymphoma classification - from controversy to consensus, the R.E.A.L. and WHO classification of lymphoid neoplasm. **Ann Oncol** 11, 3-10.
- Harris NL, Jaffe ES, Stein H, Banks PM, Chan JK, Cleary ML, Delsol G, De Wolf-Peters C, Falini B, and Gatter KC (1994) A revised European-American classification of lymphoid neoplasms, a proposal from the International Lymphoma Study Group. **Blood** 84, 1361-1392.
- Hochster HS, Kim KM, Green MD, Mann RB, Neiman RS, Oken MM, Cassileth PA, Stott P, Ritch P and O'Connell MJ (1992) Activity of Fludarabine in previously treated non-Hodgkin's lymphoma, results of an Eastern Cooperative Group Study. **J Clin Oncol** 10, 28-32.
- Hoffman M, Tallman MS, Hakimian D, Janson D, Hogan D, Variakogis D, Kuzel T, Gordon LI and Rai K (1994) 2-Chlorodeoxyadenosine is an active salvage therapy in advanced indolent non-Hodgkin's lymphoma. **J Clin Oncol** 12, 788-792.
- Horning SJ (1993) Natural history of and therapy for the indolent non-Hodgkin's lymphomas. **Semin Oncol** 20, 75-88.
- Iannitto E, Barbera V, Quintini G, Cirrincione S and Leone M (2002) Hepatosplenic T-cell lymphoma, complete response induced by treatment with Pentostatin. **Brit J Haematol** 117, 995-99.
- Keating MJ, O'Brien S, Lerner S, Koller C, Beran M, Robertson LE, Freireich EJ, Estey E and Kantarjian H (1998) Long-term follow-up of patients with CLL receiving Fludarabine regimens as initial therapy. **Blood** 92, 1165-1171.
- Koller CA, Stetson PL, Nichamin LD, Mitchell BS (1980) An assay of deoxyadenosine and adenosine in human plasma by HPLC. **Biochem Med** 24, 179-184.
- Ladetto M, Corradini P, Vallet S, Benedetti F, Vitolo M, Martelli M, Brugiattelli M, Coser P, Perrotti A, Majolino I, Fioritoni G, Morandi S, Musso M, Zambello R, Chisesi T, Di Renzo N, Vivaldi P, De Crescenzo A, Gallamini A, Salvi F, Santini G, Boccomini C, Sorio M, Astolfi M, Drandi D, Pileri A and Tarella C (2002) High rate of clinical and molecular remission in follicular lymphoma patients receiving high-dose sequential chemotherapy and autografting at diagnosis, a multicenter, prospective study by the Group Italiano Trapianto Midollo Osseo (GITMO). **Blood** 100, 1559-1565.
- Lathia C, Fleming GF, Meyer M, Ratain MJ, Whitfield L (2002) Pentostatin pharmacokinetics and dosing recommendations in patients with mild renal impairment. **Cancer Chemother Pharm** 50, 121-126.
- McLaughlin P, Hagemeister FB, Romaguera JE, Sarris AH, Pate O, Younes A, Swan F, Keating M and Cabanillas F (1996) Fludarabine, Mitoxantrone and Dexametasone, an effective new regimen for indolent lymphoma. **J Clin Oncol** 14, 1262-1268.
- McLaughlin P, Hagemeister FB, Swan F, Jr, Cabanillas F, Pate O, Romaguera JE, Rodriguez MA, Redman JR and Keating M (1994) Phase I study of the combination of Fludarabine, Mitoxantrone and Dexametasone in low-grade lymphoma. **J Clin Oncol** 12, 575-579.

- Mercieca J, Matutes E, Dearden C, MacLennan K and Catovsky D (1994) The role of Pentostatin in the treatment of T-cell malignancies, analysis of response rate in 145 patients according to disease subtype. **J Clin Oncol** 12, 2588-2593.
- Morabito F, Baldini L, Stelitano C, Luminari S, Frassoldati A, Merli F, Colombi M, Sabbatini R, Brugiattelli M, Federico M, for the Gruppo Italiano per lo Studio dei Linfomi (GISL) (2002) Prospective study of indolent non-follicular non-Hodgkin's lymphoma, validation of Gruppo Italiano per lo Studio dei Linfomi (GISL) prognostic criteria for watch and wait policy. **Leuk Lymph** 43, 1933-38.
- Morabito F, Callea I, Console G, Stelitano C, Sculli G, Filangeri M, Oliva B, Musolino C, Iacopino P, Brugiattelli M (1997) The in vitro cytotoxic effect of Mitoxantrone in combination with Fludarabine or Pentostatin in B-cell chronic lymphocytic leukemia. **Haematologica** 82, 560-65.
- Redman JR, Cabanillas F, Velasquez WS, McLaughlin P, Hagemester FB, Swan F, Jr, Rodriguez MA, Plunkett WK, and Keating MJ (1992) Phase II trial of Fludarabine phosphate in lymphoma, an effective new agent in low-grade lymphoma. **J Clin Oncol** 10, 790-794.
- Robak T, Blonski JZ, Kasznicki M, G_ra-Tybor J, Dwilewicz-Trojaczek J, Boguradzki P, Konopka L, Ceglarek B, Sulek J, Kuliczowski K, Wolowiec D, Stella-Holowiecka B, Skotnicki AB, Nowak W, Moskwa-Sroka B, Dmoszynska A and Calbecka M (2001) Cladribine combined with Cyclophosphamide and Mitoxantrone as front-line therapy in chronic lymphocytic leukemia. **Leukemia** 15, 1510-16.
- Rowland M, Tozer TN (1995) Clinical pharmacokinetics, concepts and applications (3rd Edition). Baltimore, Williams & Wilkins.
- Schouten HC, Colombat P, Verdonck LF, Gorin NC, Bjorkstrand B, Taghipour G, Goldstone AH (1994) Autologous bone marrow transplantation for low-grade non-Hodgkin's Lymphoma, the European Bone Marrow Transplantation Group experience. **Ann Oncol** 5(suppl 2), S147-149.
- Seymour JF, Grigg AP, Szer J and Fox RM (2001) Fludarabine and Mitoxantrone, effective and well tolerated salvage therapy in relapsed indolent limphoproliferative disorders. **Ann Oncol** 12, 1455-1460.
- Tobinai K, Shimoyama M, Tajima K, Kozuru M, Tomonaga M, Araki K, Kasai M, Takatsuki K, Tara M, Hotta T et al (1995) Deoxycoformycin containing combination chemotherapy for adult T-cell leukemia-lymphoma (ATL), Japan Clinical Oncology Group (JCOG) Study 9109. **Proceedings ASCO** 14, A1217 (meeting abstract).
- Waselenko JK, Grever MR, Beer M, Lucas MA, Byrd JC (2000) Pentostatin (Nipent) and Chlorambucil with granulocyte-macrophage colony-stimulating factor support for patients with previously untreated, treated and Fludarabine-refractory B-cell chronic lymphocytic leukemia. **Semin Oncol** 27 (2, suppl 5), 44-51.
- Weiss MA (2000) A phase I and II study of Pentostatin (Nipent) with Cyclophosphamide for previously treated patients with chronic lymphocytic leukemia. **Semin Oncol** 27 (2 suppl 5), 41-43.



Dr. Federico Massimo