Reduced-dose cladribine (2-CdA) plus mitoxantrone is effective in the treatment of mantle-cell and low-grade non-Hodgkin's lymphoma

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Abstract

Cladribine (2-chlorodeoxyadenosine) (2-CdA) has been shown to be effective in mantle-cell (MCL) and low-grade lymphomas (lgNHL). The aim of this multicentre study was to evaluate the rate and duration of remissions and to examine the toxicity of the combination of reduced-dose 2-CdA and mitoxantrone (CdM) in MCL and lgNHL as first-line therapy or for patients in their relapse. A total of 285 courses, median of five courses per patient, were administered to 62 evaluable patients (42 previously untreated, 20 relapsed) with 5 mg/m^2 2-CdA per day given as an intermittent 2-h infusion over 3 consecutive days combined with 8 mg/m^2 mitoxantrone on days 1 and 2 for the untreated patients or 12 mg/m^2 mitoxantrone on day 1 for patients in their first relapse for a maximum of six cycles every four weeks. 32 follicular, 18 MCL, 9 lymphoplasmacytoid, 2 marginal zone and 1 unclassified low-grade B-cell lymphoma were involved in the study. 56 of the 62 patients responded to CdM resulting in an overall response rate of 90% (95% confidence interval (CI), 80–96%) with a complete remission (CR) rate of 44% (95% CI, 31–57%) and a median duration of remission of 25 months (range 6–42+). The overall survival rate at 48 months was 80%. For 42 previously untreated patients, the overall response rate was 88% (95% CI, 74–96%) with a CR rate of 38% (95% CI, 24–54%), whereas the response rate for the group of 20 previously treated patients was similar with a 95% overall response (95% CI, 75–100%) and a CR rate of 55% (95% CI, 32–77%). In MCL, CdM showed a high activity, achieving a response rate of 100% (95% CI, 81–100%) with a CR rate of 44% and a median duration of remission of 24 months (range 6–35+). Myelosuppression was the major toxicity with 23% grade 3 granulocytopenia and 50% grade 4. Thrombocytopenia was less commonly observed, with only 8% grades 3 and 4. These results demonstrate that the combination of reduced-dose 2-CdA and mitoxantrone is a highly active regimen in the treatment of low-grade lymphomas, and in particular of MCL. © 2002 Elsevier Science Ltd. All rights reserved.

Keywords: Cladribine; Mitoxantrone; Low-grade lymphoma; Mantle-cell lymphoma

1. Introduction

Low-grade non-Hodgkin's lymphomas (lgNHL) compose a heterogenous group of indolent neoplasms.

The optimal therapeutic approach for patients with lgNHL remains controversial. Despite the fact that these malignancies are sensitive to standard chemotherapy with a relatively long survival of being observed of 5–10 years, no curative treatment modalities are, as yet, available. Nevertheless, chemotherapy with alkylating agents is the standard first-line therapy, but there is no standard salvage treatment for patients with

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relapsing or refractory disease. Even more aggressive regimens including anthracyclines do not have the potential to change the course of the disease in a crucial way [1].

Mantle-cell lymphomas (MCL) were proposed as a new entity by the Revised European-American Classification of Lymphoid Neoplasms (REAL) [2]. Patients with MCL are resistant to current therapeutic strategies and have the shortest survival of all lymphoma entities with a median survival time of 3–4 years, whatever the initial treatment used [3,4].

Therefore, new treatments are necessary to further improve on the current prospects of patients with lgNHL or MCL. Purine analogues, such as fludarabine and cladribine (2-CdA), represent newer drugs with significant activity in lgNHL showing higher response rates with more complete remissions (CRs) than alkylating agents [5] and these have also been demonstrated to have single-agent activity in unfavourable MCL [6–11]. However, no single agent is likely to make a substantial impact on the survival of patients with lgNHL. Future studies should therefore focus on combining purine analogues with other agents that are active in lgNHL. Because of their minimal non-haematological toxicities, purine analogues can be easily included into multi-agent regimens. Mitoxantrone, an anthracenedione, has been demonstrated to be effective in lgNHL [12–15]. It functions as a DNA damaging agent that intercalates DNA and causes inter- and intrastrand cross-linking, which results in cell death. 2-CdA is known to induce an imbalance in the deoxyribonucleotide pool and is therefore postulated to be a potent inhibitor of DNA repair [16]. The combination of a DNA damaging agent with an inhibitor of DNA repair and the high activity of 2-CdA and mitoxantrone when used as single agents in lgNHL as well as their individual favourable toxicity profiles suggested that they may be used in combination. Furthermore, supporting this hypothesis, we were able to demonstrate in a preclinical study synergistic effects between 2-CdA and mitoxantrone on the induction of apoptosis in lymphoma cells *in vitro* [17].

Saven and colleagues were the first to show in a dose escalation study that 2-CdA can be combined with mitoxantrone in the treatment of lgNHL. They used 0.1 mg/kg/day of 2-CdA given over 7 days by continuous infusion [18]. Recently, a few studies have proposed that a reduced dose of 2-CdA may reduce late toxicity, while maintaining the antitumour activity of standard-dose 2-CdA [19,20].

2. Patients and methods

Based on the results of these studies, and on the potential synergy between 2-CdA and mitoxantrone

(CdM), we used a reduced dose of 2-CdA (see Section 2.2). Furthermore, to render a future randomised comparison of CdM with MCP (mitoxantrone, chlorambucil, prednisone) possible, an established regimen for lgNHL in Germany, we choose to use the equivalent dosage of mitoxantrone. A modified MCP combination named PmM (prednimustine, mitoxantrone) was proved by the German low-grade lymphoma study group to be superior to cyclophosphamide, vincristine, prednisone (CVP) [21].

The study was a prospective open phase II trial starting in July 1997 in 19 participating centres. It was approved by the ethics committee of the University Hospital of Frankfurt. All patients gave written informed consent. The study was performed in keeping with good clinical practice.

2.1. Eligibility

Patients were eligible if they had a histologically-confirmed diagnosis of mantle cell or low-grade lymphoma including the following subtypes: follicular, lymphoplasmacytoid (Waldenstroem̓s macroglobulinaemia), and marginal zone. To classify the lymphoid neoplasms, we used the REAL Classification [2]. All lymph node, bone marrow and other specimen biopsies were reviewed by one of five German referral centres for haematopathology. Patients were required not to have received prior chemotherapy or to have a first relapse after pretreatment with radiotherapy or one chemotherapy regimen not containing purine analogues and to have a performance status of $\leqslant 2$ and be aged older than 18 years. Patients were staged using the Ann Arbor classification and the following staging procedure: physical examination, routine blood count, serum chemistry, serum immunoelectrophoresis and determination of immunglobulin levels, CD4-positive lymphocytes, chest X-ray, computed tomography (CT) scan of the chest, abdomen and pelvis, sonography of the abdomen, bone marrow aspiration and biopsy. In cases of clinical relevance, endoscopy of the gastrointestinal tract (GIT) was performed. Patients were classified according to the International Prognostic Index (IPI) [22]. Patients with stages III or IV in need of treatment as defined by an impairment of haematopoiesis (Hb < 110 g/l, granulocyte count $< 1.0 \times 10^9$/l, thrombocyte count $< 100 \times 10^9$/l), presence of B-symptoms, other disease-related symptoms, such as bulky disease with dislodgement of internal organs, or progressive disease were eligible for entry into the study.

2.2. Treatment

2-CdA was administered at a dose of 5 mg/m^2 per day over 3 consecutive days using a 2-h intravenous (i.v.) infusion. Mitoxantrone was given at a dose of 8 mg/m^2 per day on days 1 and 2 for untreated patients or at a

dose of 12 mg/m^2 per day on day 1 for patients in first relapse. Treatment was repeated every 4 weeks for a maximum of six cycles and was discontinued for cases that achieved a CR before the sixth cycle, had progression of disease, severe side-effects, or a persistent decrease of CD4-positive lymphocytes below 100/μl. No prophylactic antibiotic treatment including pneumocystis carinii pneumonia prophylaxis, and no granulocyte-colony stimulating factor (G-CSF) support was given.

2.3. Criteria for response and toxicity

A CR was defined as the disappearance of all measurable disease (lymph node size < 1 cm) and a return to normal blood counts, as well as a bone-marrow lymphocyte percentage < 30% in aspiration and biopsy material and no evidence of abnormal lymphoid infiltration. Partial response (PR) required a more than 50% reduction of measurable disease manifestations and a more than 50% improvement of all abnormal blood counts. Progression was defined as a > 25% increase in measurable disease with one of the following criteria: More than 25% increase of circulating lymphocytes above remission values, corresponding enlargement of lymph nodes, liver or spleen, appearance of new enlarged lymph nodes, reappearance or increasing infiltration in the bone marrow, or recurrence of B-symptoms. Treatment-related toxicity was evaluated according to World Health Organization (WHO) criteria. Blood counts, including differential, were performed weekly. Immunophenotyping of lymphocytes was performed before each cycle. Duration of remission was assessed through clinical and radiological examinations, sonographies, as well as blood counts, at three monthly intervals until relapse. Bone marrow biopsy was repeated every 6 months as part of the response evaluation procedure.

2.4. Statistical methods

Overall survival (OS) was calculated from the first day of treatment to death. Duration of remission and relapse-free survival (RFS) was calculated as the period from the beginning of remission to disease progression. Patients who died without evidence of lymphoma were censored at the time of death. Survival curves were estimated by the Kaplan–Meier method and the log-rank test was applied for comparison. Tests were two-sided and the level of significance was a P value of less than 0.05.

3. Results

3.1. Patient characteristics

66 patients entered the study between July 1997 and March 1999. 4 patients were not evaluable due to a

protocol violation: 1 patient entered the study with three prior therapies, 2 patients had high grade lymphomas and one a peripheral T-cell lymphoma. The characteristics of the 62 evaluable patients (assessable for response and toxicity) are shown in Table 1. Pre-treatment was in 8 cases with CHOP or CHOP-like regimens, in 4 cases with COP, in 4 cases with chlorambucil plus prednisone, and in 4 cases with radiotherapy. Indications for treatment were in 33 cases rapid progression of the disease, in 29 cases B-symptoms, in 41 cases a large tumour mass, in 15 cases peripheral cytopenias, mostly anaemias, and in 32 cases tumour-related pain or other disease-related symptoms.

3.2. Response

Overall, 285 cycles of therapy were applied with a median of five cycles to each patient (range 1–6 cycles). The overall response rate (ORR) in the total group of 62 assessable patients was 90% (95% Confidence Interval (CI), 80–96%) with a CR rate of 44% (95% CI, 31–

Table 1
Patient characteristics

Patients	62
Male/female	34/28
Age (years)	
Median (range)	59 (31–76)
Stages	
III (A, B)	17 (11A, 6B)
IV A	22
IV B	23
Prior therapy	
Untreated	42
First relapse	20
Histology	no. (un-/pretreated)
Follicular	32 (26/6)
Mantle cell	18 (9/9)
Lymphoplasmacytoid	9 (4/5)
Marginal zone (MALT)	2 (2/0)
Unclassifiable low-grade B-cell	1 (1/0)
Prognostic factors	
Performance status > 2	0
Extranodal involved sites > 1	14
LDH > 200 U/l	30
Age > 60 years	28
Stage III or IV	62
Beta-2-microglobulin > 2.0 mg/dl[a]	29
B-symptoms	28
Bone marrow involved	28
Gastrointestinal tract involved	8
Bulky disease (⩾ 5 cm)	31
Prognostic groups (IPI)	
Low risk (1 risk factor)	18
Low intermediate risk (2 risk factors)	26
High intermediate risk (3 risk factors)	15
High risk (4–5 risk factors)	3

MALT, mucosa-associated lymphoid tissue; LDH, lactate dehydrogenase.
[a] Data evaluable for 43 patients.

57%) and a PR rate of 47% (95% CI, 34–60%) (Table 2).

The median duration of remission was 25 months (range 6–42+ months) with 25 patients still in ongoing remission. 31 patients have relapsed to date after 6–38 months (Fig. 1). There was no correlation between response and elevated beta-2-microglobulin ($P = 0.10$), elevated lactate dehydrogenase (LDH) ($P = 0.18$), and no statistical difference in the duration of RFS between CRs and PRs ($P = 0.25$) with times of 25 and 24 months, respectively, nor between previously untreated (31 months) and pretreated patients (21 months) ($P = 0.09$). The ORR for the 42 untreated patients was 88% (95% CI, 74–96%) and for the 20 pretreated patients 95% (95% CI, 75–100%), with only 1 pretreated patient not responding to therapy.

The ORR in 9 patients with lymphoplasmacytoid lymphomas (Waldenstroem's macroglobulinaemia) was
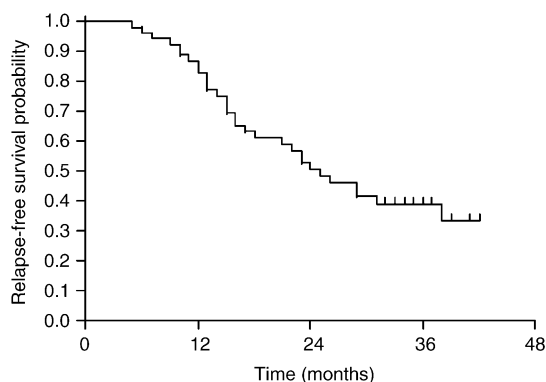

Fig. 1. Relapse-free survival for all patients entering Complete Remission (CR) or Partial Response (PR) (Kaplan–Meier method).

100% (95% CI, 66–100%), while only 26 out of 32 patients with follicular lymphomas responded to CdM reaching a response rate of 81% (95% CI, 64–93%) (Table 2).

Most responses were evident after two courses of chemotherapy. 48 patients responded to CdM after the second, 4 patients after the third, and 4 patients after the fourth cycle. In 9 responding patients, therapy was prematurely stopped after two or three courses and only 2 of them achieved a CR. 22 patients received two to four courses and 34 patients received five or six cycles achieving CR rates of 32 and 56%, respectively. RFS between both groups was not different, while OS differed significantly ($P = 0.02$) in favour of patients having received five or six courses of CdM.

Up until now 12 patients, 5 of them pretreated, have died: 2 patients with follicular lymphomas refractory to CdM and to subsequent salvage therapies, 1 patient with histological transformation to a high-grade lymphoma, 7 patients due to progressive disease suffering from recurrent relapses, 1 patient with prior chlorambucil therapy due to a secondary neoplasia and pulmonary embolism suffering from an oesophageal cancer being in his second PR for 7 months, and 1 patient with a previously known coronary heart disease due to myocardial infarction being in PR for 6 months. The overall survival curve for all patients is shown in Fig. 2. The median duration of survival has not yet been reached, the actuarial survival rate at 48 months is 80%. 44 patients (71%) were in the low or low-intermediate risk group and 18 patients (29%) in the high-intermediate or high-risk group when applying the IPI for NHL [22]. OS between these risk groups was significantly different ($P = 0.0007$) with a hazard ratio of 6.1, which means

Table 2
Treatment results

Entity	Pts no.	CR no. (%)	PR no. (%)	CR + PR no. (%)	Rem. dur. months	OS at 36 months (%)
Follicular	32	15 (47)	11 (34)	26 (81)	29	87
Previously untreated	26	10 (38)	11 (42)	21 (81)	–	–
Pretreated	6	5 (83)		5 (83)	–	–
Mantle cell	18	8 (44)	10 (56)	18 (100)	24	68
Previously untreated	9	3 (33)	6 (67)	9 (100)	–	–
Pretreated	9	5 (56)	4 (44)	9 (100)	–	–
Lymphoplasmacytoid	9	1 (11)	8 (89)	10 (100)	–	–
Previously untreated	4		4 (100)	4 (100)	–	–
Pretreated	5	1 (20)	4 (80)	5 (100)	–	–
Marginal zone, previously untreated	2	2		2 (100)	–	–
Unclassifiable low-grade B-cell, previously untreated	1	1			–	–
All previously untreated	42	16 (38)	21 (50)	37 (88)	31	82
All pretreated	20	11 (55)	8 (40)	19 (95)	21	71
Total						
All patients	62	27 (44)	29 (47)	56 (90)	25	80

CR, complete response; PR, partial response; Rem. dur., Median duration of remission; OS, overall survival rate; – statistical tests were not done due to the low statistical power because of the small numbers involved; Pts, patients.
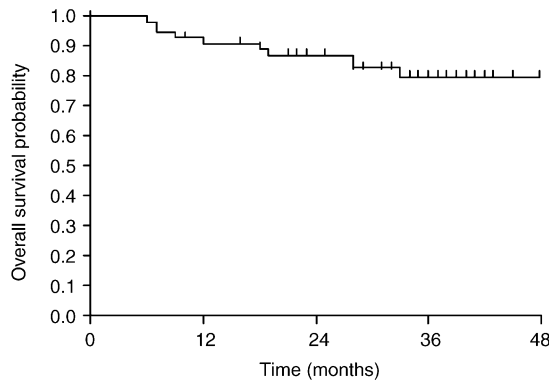
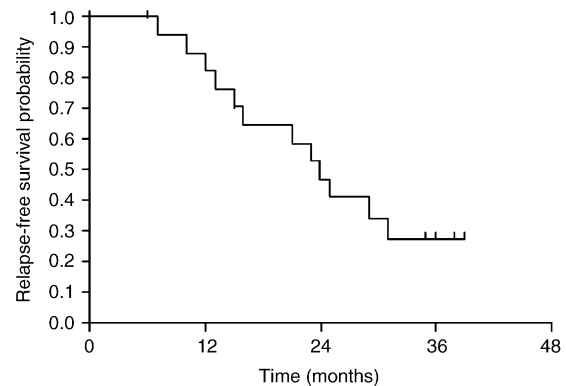Fig. 2. Overall survival for all patients (Kaplan–Meier method).

Fig. 3. Relapse-free survival for all patients with mantle cell lymphomas (Kaplan–Meier method).

Fig. 4. Overall survival for all patients with mantle cell lymphomas (Kaplan–Meier method).

that on average patients of the higher risk group die at 6 times the rate of patients with a lower risk. In univariate analyses survival was statistically different for age ($P=0.011$), showed a trend towards significance for LDH ($P=0.059$) while for beta-2-microglobulin ($P=0.36$) no difference was found. Differences in the duration of OS between patients with CRs and PRs ($P=0.027$) were statistically significant, while no such statistical differences were observed between previously untreated and pretreated patients ($P=0.093$).

3.3. Response in the mantle cell lymphomas

18 patients with MCL, nine of them entering the study in their first relapse, were treated with CdM. Pretreatment was in 4 cases with CHOP, in 4 cases with COP, and in 1 case with radiotherapy. The median age of the 13 men and 5 women was 65 years (range 49–76 years). 5 patients had stage III, 13 patients had stage IV disease with bone marrow involvement, and 4 patients had additional involvement of the upper and lower GIT. According to the IPI, 10 patients (56%) were in low or low-intermediate risk group, and 8 patients (44%) in the high-intermediate or high-risk group.

All 18 patients with MCL achieved a remission yielding to an ORR of 100% (95% CI, 81–100%). CR occurred in 8 patients (44%), in 3 of 9 previously untreated (33%) and in 5 of 9 pretreated patients (56%) (Table 2). Two out of 4 patients with both bone marrow and GIT involvement achieved a CR lasting 10 and 16 months. The median duration of remission was 24 months (Fig. 3), with 6 patients still in ongoing remission (range, 6–39+ months). 13 patients are still alive (range 22–40+ months). The actuarial survival rate at 36 months is 68% (Fig. 4).

3.4. Toxicity

Non-haematological toxicity was generally mild, mainly restricted to WHO grades 1 and 2 (Table 3). 9 patients suffered from a remarkable parageusia, which
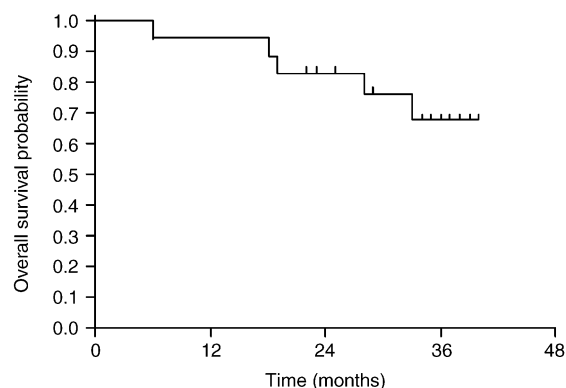
was always spontaneously reversible, lasting for 5 days on average in between the therapy cycles. Only 2 patients experienced grade 3 alopecia. One patient had a deep venous thrombosis, which could be treated successfully. There were no treatment-related deaths. Granulocytopenia was the most common side-effect noted. Grade 3 occurred in 66 (23%) and grade 4 in 142 (50%) of the 285 evaluable cycles, with a median granulocyte nadir on day 12. There was no evidence of cumulative myelosuppression for granulocytes, except for one patient. Two bacterial pneumonias during a granulocytopenic phase, eight localised *herpes zoster* infections, and one subcutaneous (s.c.) abscess with micrococcus species (*Gaffkya*) have been observed. Grade 3 or 4 thrombocytopenia occurred less often in only 13 (5%) and 11 (4%) of all the evaluable cycles, respectively. CD4-positive lymphocytes, documented in 43 patients, with a median of only 371/μl before treatment decreased to 142/μl after two, 117/μl after four, and 93/μl after six cycles. Treatment was prematurely discontinued in one case after two cycles due to persisting leuco- and thrombocytopenia, and in 6 cases due to prolonged CD4-positive lymphocytopenia below 100/μl (criterion for discontinuation according to protocol): in

Table 3
Toxicity based on number (and %) of all patients

WHO grade	I/II (%)	III (%)	IV (%)
Leucocytopenia	1	9 (15)	50 (81)
Granulocytopenia	1	12 (19)	46 (74)
Thrombocytopenia	15 (24)	8 (13)	8 (13)
Anaemia	35 (56)	7 (11)	0
Viral infection	10 (16)	0	0
Bacterial infection	3 (5)	0	0
Nausea/vomiting	15 (24)	2	0
Polyneuropathy	6 (10)	0	0
Lung (pleural fluid, dyspnoea)	0	1	0
Hair loss	9 (15)	2	0
Parageusia	9 (15)	0	0
Diarrhoea	5 (8)	0	0
Stomatitis	3	0	0

WHO, World Health Organization.

3 cases each after three and four cycles. No difference in the toxicity profiles was found between patients with mantle cell lymphomas and other entities. Two male patients developed secondary malignancies, one oesophageal cancer and one non small-cell lung cancer in a patient with a smoking history, 6 and 29 months, respectively after the initiation of therapy with CdM. No other significant infections have been seen after the cessation of therapy after reaching a stable response or in the time interval when a salvage therapy had to be initiated for a recurrence.

4. Discussion

The study demonstrates that the combination of dose-reduced 2-CdA and mitoxantrone is a highly active regimen in the treatment of lgNHL and MCL. 90% of the 62 patients responded to therapy with a CR rate of 44% and a median remission duration of 25 months. Myelosuppression was the major toxic event of treatment with granulocytopenias (grade 3 or 4) occurring in 23 and 50% of all cycles, respectively. Due to the addition of mitoxantrone, the haematological toxicity of CdM was more prevalent than in our previous experience with 2-CdA monotherapy, in which we observed grade 3 or 4 granulocytopenias in only 14 and 3%, respectively [23]. No G-CSF support was given in both studies. Despite the haematological toxicity, the incidence of infections was rather low, with only two patients (3%) experiencing bacterial pneumonias. Otherwise, CdM was well tolerated by most patients with no acute non-haematological toxicities and no treatment-related deaths or other severe infectious complications.

Several phase II trials with purine analogue-containing regimens are reported in the literature showing promising activity in the treatment of lgNHL. Only a few experiences are available for combination regimens including 2-CdA. Two studies report results of 2-CdA combined with mitoxantrone and dexamethasone or prednisone using a standard dose of 2-CdA [18,24]. In both studies, with heavily pretreated patients, the risk for infectious complications was in the range of 35%. Saven and colleagues in a later study omitted prednisone from the regimen, since it exacerbated the risk of serious infections without improving response rates. They recommended a reduced dose of 2-CdA, applying it as a continuous infusion with 0.075 mg/kg/day for 7 days, and to retain the dose of mitoxantrone at 5 mg/m^2 on day 1 [18]. In combination with alkylating agents, 2-CdA was studied in three trials [25–27]. Myelosuppression, mostly thrombocytopenia, was the limiting factor when 2-CdA was combined with chlorambucil or cyclophosphamide. Furthermore, a greater risk for pulmonary aspergillosis and other severe opportunistic infections was observed [27]. Fludarabine has been studied in combination with mitoxantrone with or without corticosteroids, with cyclophosphamide or with both agents [28–33]. Because of the low numbers of patients and different patient populations, the parameters influencing the results having changed from one report to another. In addition, the limited comparability of phase II studies means it is difficult to compare these heterogeneous trials with our study. So far, it can be concluded that purine analogues combined with other cytotoxic agents such as cyclophosphamide, chlorambucil or corticosteroids are associated with an increasing risk of infectious complications, but also with high response rates in the range of 72–94% and in one study of up to 100% [25,27,28,30,32–35].

Therapies with purine analogues are clearly immunosuppressive with a significant drop and long-term suppression of the CD4-positive lymphocyte counts. We wished to decrease the immunosuppression associated with 2-CdA by reducing the dose of 2-CdA from 5 to 3 days, with 5 mg/m^2 given per day. However, the median count of CD4-positive lymphocytes decreased throughout the treatment period. As a result of this depressed cell-mediated immunity, we observed eight localised *herpes zoster* infections. Although the results in this study were not directly comparable with our previous study with 2-CdA monotherapy [23], we found no difference in the decrease of CD4-counts between the two studies. This is in accordance with recently published studies, when reduced dosages of 2-CdA were used [19]. Conversely, with lower-dosages of 2-CdA, these studies were able to diminish the rate of infections, while maintaining a similar antitumour activity compared with standard-dose 2-CdA studies [19,20].

In our previous study with 2-CdA applied as monotherapy, we were not able to induce prompt responses in all cases, first observing a response to treatment after five cycles of 2-CdA in 11 patients [23]. In contrast to this previous experience, we observed no such delayed response to therapy with CdM. Thus, 2–4 courses were

sufficient to induce response in this study. However, a continuation of therapy after remission is obtained seems to be necessary as we observed more CRs and a significantly longer OS in patients who had no early discontinuation of therapy having received five or six cycles of CdM.

In the present trial, the dosage of mitoxantrone was reduced to 12 mg/m^2 on day 1 in previously treated patients to avoid severe haematological toxicity. Since the response rates were similar for previously untreated and pretreated patients (88 and 95%) in this study and no difference in the duration of RFS and OS was seen between the groups, we can conclude that dose of 12 mg/m^2 mitoxantrone on day 1 only is sufficient in combination with 2-CdA.

The majority of patients with MCL have a different clinical presentation than patients with lgNHL. They usually present with advanced disease, pursue an aggressive clinical course [36], and are resistant to current therapeutic strategies having the shortest survival, whatever the initial treatment was used [3,4]. Even high-dose therapy has not been shown to improve survival [37]. The purine analogues were reported to have some single-agent activity in MCL. Recent studies suggest that fludarabine is moderately effective in this entity reaching response rates of 33, 41 and 63%, respectively [6–8]. The observed response rates of 58, 63 and 81% in phase II studies using 2-CdA seem to be higher than with fludarabine [9–11]. Patients with MCL in our study presented with an older age (median of 65 years) and more advanced disease, with 8 patients (44%) having 3–5 risk factors according to the IPI. The remaining group of 44 patients with lgNHL had a median age of 57 years and only 10 cases (23%) had 3–5 risk factors. The toxicity profile of CdM was not different between the elderly patients with mantle cell lymphomas and the other subgroups. Despite the unfavourable prognostic factors of the 18 MCL patients treated with CdM in our study, all of the patients responded to therapy, with a CR-rate of 44% and a median duration of remission of 24 months.

Encouraged by the favourable response rates achieved with CdM in lgNHL and MCL, we have initiated a phase III study to compare CdM with a standard regimen consisting of chlorambucil, mitoxantrone and prednisone (MCP). Our data indicate, that CdM may broaden the range of therapeutic options in lgNHL, and in particular for MCL.

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