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Cladribine as monotherapy or combined with dexamethasone and idarubicin or mitoxantrone in previously treated patients with low-grade lymphoid malignancies

We compared efficiency and toxicity of cladribine (2-CdA) in monotherapy and in combination with dexamethasone and mitoxantrone (CMD) or idarubicin (CID) in pretreated patients with low grade NHL. We have shown that 2-CdA has significant activity in this disease but the addition of dexamethasone and anthracyclines may not be of advantage compared to 2-CdA alone.

Sir,

The long-term prognosis for patients with advanced relapsed or refractory low grade non-Hodgkin's lymphoma (LGNHL) remains poor. Therefore many new therapeutic approaches including new chemotherapy agents and new combinations regimens have been evaluated.

In this report we present our experience with the new purine analog 2-chlorodeoxyadenosine (2-CdA) used as monotherapy and combined with dexamethasone and mitoxantrone (CMD) or dexamethasone and idarubicin (CID) in patients with LGNHL.

This study was an open phase II single institution trial initiated in January 1996 and closed in April 1999. Criteria for entry into the study included a histologic diagnosis of LGNHL,[1] and advanced stage of refractory or relapsed disease. All patients had received at least three prior regimens of chemotherapy for NHL.

2-CdA was given at a dose 0.12 mg/kg in a 2-hour intravenous infusion, on days 1-5. In the CMD program mitoxantrone 10 mg/m^2 i.v., day 1 and dexamethasone 20 mg p.o., days 1-5, were added to 2-CdA. In the CID program idarubicin 12 mg/m^2 i.v., day 1 was given. The cycles were repeated at 4-week intervals in most cases.

Table 1. Patient characteristics.

	2-CdA	*CMD*	*CID*
Number of patients	36	17	5
Age (years)			
Median	63	61	60
Range	35-75	32-69	48-70
Sex (male/female)	23/13	10/7	2/3
Histology			
B-cell lymphocytic	20	9	1
Prolymphocytic	1	4	2
Lymphoplasmocytic	12	3	2
Centroblastic/centrocytic	3	1	0
Ann Arbor stage			
III	7	1	0
IV	29	16	5
B symptoms	28	18	5
Bone marrow involvement	19	9	3
Elevated LDH level	18	10	4
International Prognostic index			
3	1	0	0
4	30	13	4
5	5	3	1
Pre-treatment duration, years			
Median	4.5	3	4
Range	1-8	2-7	2-6
Prior course of chemotherapy			
Median	6.5	7	6
Range	5-10	5-11	3-8
Prior radiotherapy	21	9	2

Complete and partial responses (CR and PR) were defined as reported elsewhere.[2] Toxic effects were monitored and assessed according to the WHO criteria.[3]

Fifty-eight patients entered the study. Thirty-six of them were treated with 2-CdA alone, 17 received chemotherapy according to the CMD regimen and 5 according to the CID program. The characteristics of the patients are listed in Table 1.

Of the 36 patients treated with 2-CdA alone 13 (36.2%) responded. The median duration of CRs was 12 months (range from 7 to 48 months) and the median duration of PRs was 6 months. The CRs were observed after a median of 4 cycles and PRs after a median of 3 cycles of 2-CdA.

Of the 17 patients treated with CMD, 7 (41.2%) responded. The CRs were observed after 2 and 3 cycles of CMD and lasted 13 and 8+ months. PRs were observed after a median of 2 cycles of 2-CdA and their median duration was 7 months.

Among the 5 patients treated with CID we observed 1 CR and 1 PR which lasted, respectively, 6+ and 5 months. Both CR and PR were observed after 2 courses of CID. Table 2 summarizes the patients' responses.

Both 2-CdA and CMD (or CID) programs were well tolerated. The major toxicity was myelosuppression. Grade 3 or 4 thrombocytopenia occurred in 36.5% of patients treated with 2-CdA and 34% treated with

Table 2. Response according to the treatment of LGNHL with 2-CdA, CMD or CID.

Treatment	No. of patients	CR	PR	NR
2-CdA	36	4 (11.2%)	9 (25.0%)	23 (63.8%)
CMD	17	2 (11.7%)	5 (29.5%)	10 (58.8%)
CID	5	1 (20%)	1 (20%)	3 (60%)

The differences among the groups treated with the different regimens are not significant (χ^2 test) ($p>0.05$). CR: complete response; PR: partial response; NR: no response.

CMD or CID. Grade 3 or 4 neutropenia developed in 35% and 37% of patients, respectively. Infections occurred in 40% of patients treated with 2-CdA (2 patients died of sepsis) and 38% of patients treated with CMD or CID (1 patient died of sepsis)

There was one fatal neurologic complication in a patient with pre-existing paraneoplastic neurological syndrome, who died of an apparent rapidly progressive sensimotor peripheral neuropathy after completing the treatment with 2-CdA alone.

The results of our study revealed that 2-CdA as monotherapy has significant antitumor activity in previously treated LGNHL patients. The overall response rate was 36.2%. Similar effects have been observed by others.[4,5] It should be stressed that the activity of 2-CdA in previously treated LGNHL seems to be similar to that of another purine analog – fludarabine.[6,7]

There is still little experience on using new purine analogs in combination with other drugs in LGNHL treatment. Impressive results were observed by McLaughlin, using a combination of fludarabine, mitoxantrone and dexamethasone in patients with recurrent or relapsed LGNHL.[8] He recorded a 94% overall response rate with 47% CRs. The combination of 2-CdA with mitoxantrone also resulted in a high (70%) rate of responses.[9] The relatively low rate of responses observed in our patients is probably a consequence of the advanced stage of the disease and the multiple previous therapies.

In conclusion, these preliminary results suggest that addition of mitoxantrone or idarubicin and dexamethasone to 2-CdA in previously treated patients with LGNHL may not be of any advantage over 2-CdA alone.[10] However, randomized studies are necessary to confirm this.

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Key words

Low grade non-Hodgkin's lymphoma, 2-chlorodeoxyadenosine, mitoxantrone, idarubicin, combination chemotherapy

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Cyclophosphamide / cyclosporin-A treatment of multicentric Castleman's disease with Kaposi's sarcoma

We have used a combination of cyclosporin A and cyclophosphamide to treat a patient with multicentric Castleman's disease (MCD) complicated by visceral Kaposi's sarcoma (KS). Beneficial effects were observed on both MCD and KS lesions: the patient's clinical, radiological and laboratory findings have been stable for 27 months.

Sir,

Multicentric Castleman's disease (MCD) is an uncommon disorder of immune regulation characterized by constitutional symptoms, diffuse lymphoadenopathy, hepato-splenomegaly, mediastinal masses resembling thymoma that may be complicated by non-Hodgkin's lymphomas and Kaposi's sarcoma (KS).[1] The prognosis of MCD is poor with a mean survival of 27 months.[2] Very limited information is available regarding treatment[3] and no consensus exists on optimal therapy.

We describe the case of a 53-year old female whose clinical history began in 1994 with fever, peripheral and mediastinal lymphoadenopathy, and anemia.