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ORIGINAL ARTICLE

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Primary treatment of low-grade non-Hodgkin's lymphoma using an all oral anthracycline-containing regimen, chlorambucil, idarubicin, dexamethasone (CID) – a phase II study

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Abstract *Purpose*: The majority of patients with low-grade non-Hodgkin's lymphoma (LGNHL) are in the older age groups and are thus less able to tolerate aggressive treatment. Chlorambucil, alone and in combination, has been widely accepted as the initial treatment of choice for many years. The availability of an anthracycline which could be given orally in combination with chlorambucil and steroid led us to investigate the efficacy and toxicity of this novel regimen. *Methods*: Patients (age less than 70 years) with a histologically confirmed diagnosis of LGNHL (Kiel classification) were eligible for the study if they had no previous chemotherapy. Treatment consisted of chlorambucil 20 mg/m^2 daily for 3 days given on each day in three divided doses, idarubicin 10 mg/m^2 for 3 days before breakfast, and dexamethasone 4 mg twice daily for 5 days. All drugs were given orally. Treatment was repeated every 21 days for a maximum of six courses. The regimen was assessed for toxicity and response. *Results*: A total of 72 patients were registered, and 64 were eligible (median age 52 years). Toxicity was assessed for all cycles given (347). The predominant toxicity was haematological, but in only one course did grade 4 neutropenia (less than 0.5×10^9) occur. Alopecia was not a problem. Full doses of the treatment were administered to 40% of the patients, with no delays or dose reductions. The overall response rate was 83%. Six patients had static disease and two progressed on treatment. Lactate dehydrogenase (LDH) was found to be a good predictor of response to treatment. Of 12 patients documented to have raised LDH, 5 failed to respond to treatment, compared to 1 of 32 patients who had a normal LDH (χ^2 10.65, $P < 0.002$). With a minimum follow-up of 4 years for all patients actuarial 5-year event-free survival was 22% and overall survival was 65%. However, in patients with best and intermediate risk LGNHL (by the SNLG Prognostic Index for Low Grade Disease) overall survival are 88% and 64%, respectively. *Conclusions*: This novel regimen was effective and well tolerated.

Key words Low-grade NHL · Oral chemotherapy · Idarubicin

On behalf of the Therapy Working Party and Pathology Working Party of the Scotland and Newcastle Lymphoma Group (SNLG)

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Introduction

The issue of what constitutes optimum therapy for advanced low-grade non-Hodgkin's lymphoma (LGNHL) remains under constant review. The fact that the vast majority of patients in this category are in the older age groups and are less able to tolerate more aggressive treatment has led to the search for novel therapeutic approaches.

The absolute incidence of non-Hodgkin's lymphoma (NHL) is increasing at the rate of approximately 4% per annum [4], for reasons that are unexplained. LGNHL accounts for 44% of patients with NHL within the population-based Scotland and Newcastle Lymphoma Group (SNLG) with a median age at presentation of 64 years. As the population ages the absolute number of cases of LGNHL is destined to increase substantially. The natural history of initially untreated LGNHL shows

that some 23% of patients may undergo spontaneous regression and that the actuarial survival at 10 years is 73% [10]. However, in most patients, these lymphomas eventually progress with increasing lymphadenopathy, involvement of extranodal sites, and the development of systemic symptoms for which the patient must be treated. The policy of expectant treatment in the absence of such progression [2, 10] holds far more appeal for older patients than younger ones.

Chlorambucil, either alone or in combination, has been widely accepted as the treatment of choice in LGNHL for many years. The addition of vincristine and prednisolone resulted in more complete remissions [16], but results were still disappointing, and, particularly for younger patients, the search for new treatment programmes continued. In 1990 preliminary results were reported of a pilot study of mitoxantrone in combination with chlorambucil and prednisolone [12] in 15 patients with LGNHL which suggested that the addition of an anthracycline might be of some benefit. The idea of combining an oral anthracycline with chlorambucil and steroid to provide an "all oral" three-agent induction schedule for a disease which affects a predominantly elderly population, seemed appealing and led to the design of the present phase II study.

Oral idarubicin is rapidly absorbed giving peak levels about 2 h after ingestion [20]. The major metabolite, idarubicinol, has a very long half-life (over 40 h) [8], and also demonstrates cytotoxic activity, making this drug a logical choice in tumours with a slow turnover. There are two reports of oral idarubicin being used as a single agent in phase II studies in intermediate-grade NHL/LGNHL in older patients. In one study [5], using a dose of 30/35 mg/m^2 on 1 day, toxicity was mild but little efficacy was shown. In the second study [3], in which idarubicin was administered at a higher dose (45 mg/m^2) in divided doses over 3 days, responses were observed in 58% of patients. In both studies oral idarubicin was well tolerated, with myelosuppression being the dose-limiting toxicity. Following these reports, the SNLG instituted the present phase II study in patients with LGNHL (Kiel classification) using chlorambucil, oral idarubicin and dexamethasone (CID) with the intention of assessing toxicity and response relative to the different risk group categories identified by the SNLG prognostic index in this disease [15].

Patients and methods

Patients

Between July 1991 and October 1993, 72 patients with LGNHL were registered on to the study. Patient inclusion criteria were as follows:

- < 70 years of age – for the first ten patients entered.
- Performance status < 3 [11]
- LGNHL as defined according to the Kiel classification [12]
- No previous history of cardiac disease
- No previous chemotherapy for NHL

All histology was to be centrally reviewed by one of us (B.A.) on behalf of the Pathology Working Party.

Ethical approval was obtained for this study and signed informed consent was given by all participating patients. The pretreatment staging evaluation included full biochemical profile, bone marrow biopsy, chest radiograph and imaging of thorax and abdomen using computed tomography. It was recommended that lactate dehydrogenase level (LDH) be performed on all patients. Follow-up was to September 1997, i.e. a minimum follow-up of 4 years for all patients.

Treatment schedule

Patients received the treatment schedule shown in Table 1. Antiemetics, most commonly ondansetron, were given routinely during chemotherapy. Treatment was repeated at 3-week intervals for a maximum of six courses. Patients were evaluated after three courses and if there was no clinical response, a change in treatment modality was recommended. If haematological toxicity was encountered, physicians were encouraged to delay treatment for 1 week, rather than reduce the dose. After completing all six courses of chemotherapy, patients were again staged. Patients with "bulky disease" at presentation were given radiotherapy at the discretion of their physician.

Toxicity was assessed using the WHO classification [21]. All patients who registered for the study were included in the toxicity analysis.

Response criteria

Complete response (CR) was defined as the disappearance of all clinical evidence of active tumour for a minimum of 8 weeks and absence of other symptoms. CR(m) was defined as absence of all evidence of nodal involvement, minimal involvement of marrow at the end of treatment and continuing evidence of remission 1 year later. Partial response (PR) was defined as ≥50% decrease in all measured lesions; no lesions could increase in size and no new lesions could appear.

Overall survival was measured from entry to the protocol until death. For event-free survival (EFS), failure to achieve CR, relapse and death were considered as "events" from the date of starting the protocol.

Statistical analysis

Survival curves were drawn according to the Kaplan-Meier method [13] and the log-rank test was used to compare curves [18].

Results

Of 72 patients registered, 64 were enrolled in the study. The reasons for exclusion of patients were: previous chemotherapy (four), patient refused treatment having originally given consent (one), severe thrombocytopenia at entry (one), death due to myocardial infarction secondary to previously undisclosed severe angina reported as unrelated to the trial treatment by the physician in

Table 1 Treatment schedule

Chlorambucil	20 mg/m^2 daily for 3 days, orally, given each day in three divided doses
Idarubicin	10 mg/m^2 daily for 3 days, orally, after breakfast
Dexamethasone	4 mg twice-daily for 5 days

charge during course one (one) and exclusion on pathological review (transformation to high-grade lymphoma) (one). Patient presentation details are shown in Table 2. The median age of the patient group was 52 years. After the initial ten patients had been analysed, the criteria for inclusion were extended to >70 years of age if the physician felt the patient could tolerate treatment.

Response

In three patients it was impossible to assess response (one had an early death, one transformed to high-grade NHL whilst on treatment and the third developed multiple myeloma concomitantly). There were 21 CR, 12 CR(m) and 20 PR giving an overall response rate of 83%. Six patients had 'static disease' and two progressed on treatment.

With a minimum follow-up of 4 years, the overall survival (65% at 5 years) and EFS (22% at 5 years) are shown in Fig. 1. The SNLG prognostic index for patients with LGNHL [15] (which was formulated on a comparable patient group) was applied. The index (Table 3), which takes into account gender, haemoglobin level, age, performance status and stage, divides patients into three prognostic groups (best, intermediate and worst) who would be predicted to have 5-year survivals of 84%, 58% and 26%, respectively (Table 4). The responses by index in our cohort are shown in Table 5 and Fig. 2, and are 88%, 64% and 33%.

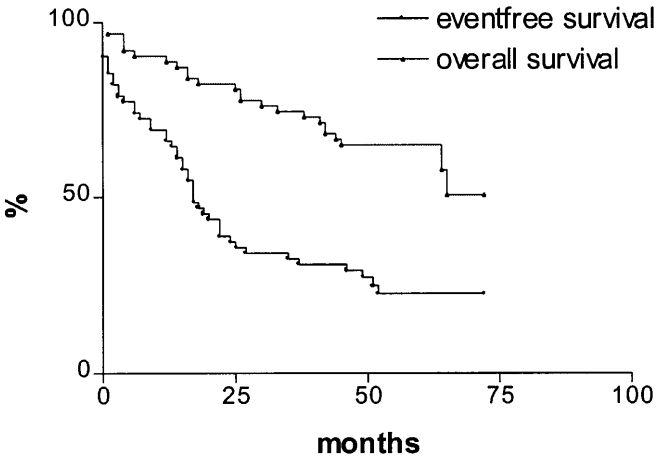

Fig. 1 Overall and event-free survival (all patients)

An abnormal LDH level was a good predictor of response. Of 12 patients who had a documented raised LDH, 5 demonstrated a lack of initial response compared to 1 of 32 patients who had a normal LDH (χ^2 10.65, $P < 0.002$).

Toxicity

Patients received a total of 347 courses of CID (52 received all of the planned six courses, range one to nine). The predominant toxicity was haematological, but WHO grade IV neutropenia was only observed in one course (see Table 6). Other toxic effects were not a major problem and were mainly attributable to steroid therapy. Nausea and vomiting occurred only in patients who had not been given antiemetic therapy, and was easily controlled once this was instituted. Alopecia occurred in one patient who experienced transient thinning of her hair. Of 283 courses, 46 (16%) were delayed, 31 by

Table 2 Patient details (all six treatment courses given to 52 patients, range one to nine)

All eligible patients	64
Sex	
Male	39
Female	25
Age (years)	
<50	26
50–69	32
>70	6
Histological subtype	
Small lymphocytic	6
Follicular	48
Mantle cell	5
Other low grade	5
Clinical stage	
2	9
3	11
4	44
LDH	
Normal	32
Elevated	12
Not done	20
Bulk disease	12
≥10 cm	7
Radiotherapy to bulk disease	7
SNLG index (see Table 4)	
Best	17
Intermediate	39
Worst	7

Table 3 Scottish and Newcastle Lymphoma Group Risk Index (SNLG index) for LGNHL (index of patient = aggregate of scores) (from Leonard et al. [15])

Presentation feature	Score
Performance status	
1, 2	1
3	2
>3	4
Age (years)	
50–65	2
≥66	4
Stage ≥2	1
Sex male	1
Haemoglobin level	Sum of other scores minus 0.27 × level (g/dl) at diagnosis

Table 4 Predicted 5-year survival in relation SNLG index

Prognostic group	Index	5-year survival (%)
Best	≤0.7–0	84
Intermediate	0–3	58
Worst	>3.0	26

1 week, 12 by 2 weeks and 13 by 3 to 4 weeks. Doses were reduced by 25% in 44 courses, by 33% in 25 courses, by 50% in 10 courses, by 66% in 3 courses and by 75% in 2 courses. However, 26 of 64 eligible patients (41%) received full doses of treatment with no delays or dose reductions. There was no significant difference in toxicity between those above and those below the median age (52 years) at presentation; i.e. toxicity was not age-related (data not shown).

Discussion

LGNHL is a malignancy with a slow but inexorable progression. Median survival at the present time is similar to that originally reported in the 1940s [7]. Chlorambucil, introduced into the treatment of the disease over 40 years ago, remains the "gold standard" single agent, but the disease, even when treated, is characterized by relapses and remissions (some spontaneous) which gives it a variable natural history [10] and makes results of treatment difficult to analyse. In addition, because the majority of patients are elderly, any new treatment combination must be tolerated in the older age group as well as having therapeutic efficacy. An intensive but well-tolerated oral combination could be of value as a therapeutic option.

Table 5 Patient details and response to therapy by SNLG prognostic category (*CR* complete response, *CR(m)* complete clinical response but repeat marrow positive, *GPR* good partial response >75%, *PR* partial response)

	Prognostic category		
	Worst	Intermediate[a]	Best
Patient nos.			
Total	7	40	17
Male	6	25	9
Female	1	15	8
Stage			
II	1	6	1
III	6	9	3
IV		25	13
Age (years)			
Median	68	58	42
Range	66–72	26–72	30–54
Response			
CR	1	13	7
CR(m)	4	5	3
GPR		6	4
PR		8	2
Static	1	5	
Progression		2	
Unassessable	1[b]		1[c]
Actuarial 5-year survival (%)	33	64	88

[a] One patient had an unrelated early death
[b] Had concomitant myeloma
[c] Transformed to high-grade NHL within 3 months

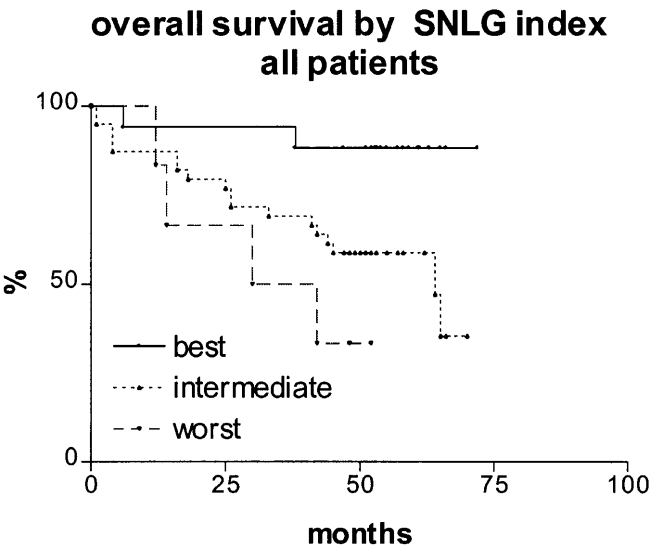

Fig. 2 Overall survival by SNLG prognostic index

In 1991, the SNLG in an effort to define the prognosis in patients with LGNHL more accurately, formulated a prognostic index to identify discreet prognostic subgroups within the "low-grade" lymphoma category [21]. Such prognostic indices have rarely been used in planning or analysing studies, though it has been noted that the international index identifies some low-grade lymphoma patients with high-risk features [9]. In the present study the SNLG index was used to put the results into the context of the risk groups. The index clearly divided patients on this study into different prognostic groups, with overall survival at 5 years of 88% and 64%, respectively, for the best and intermediate prognostic groups, but 33% for the poor-risk group, a distribution very similar to that observed in those variously treated patients from whom the index was originally derived. LDH has been reported to be of independent prognostic value in NHL [1, 6], and despite few patients (44) having their level estimated in this study, we were able to confirm on univariate analysis that LDH is of important prognostic significance.

Table 6 WHO grade toxicity (347 courses assessed)

Symptom	WHO grade toxicity				
	0	1	2	3	4
Neutropenia	185	86	47	22	1
Anaemia	329	12	4	2	0
Thrombocytopenia	340	4	2	1	0
Nausea/vomiting	304	30	8	5	0
Infection	326	5	10	6	0

Each of the three drugs in this CID regimen is individually active in lymphoma. The use in this schedule of chlorambucil at three times the "usual" daily dose, given in three divided doses, was selected on the basis of pilot information [14]. The response rate in our study within the risk categories identified by the SNLG index compares favourably with other three-drug regimens used as primary therapy [11], and the toxicity profile was acceptable.

Currently the role of the nucleoside analogues in low-grade lymphoma is attracting substantial attention. A recent report on the use of fludarabine monophosphate as a single agent, whilst demonstrating activity at a dose of 25 mg/m^2 per day, gave a CR rate of 37% and a median progression-free survival of 13.6 months [19] accompanied by substantial toxicity (9 of 54 patients had to stop treatment prematurely due to toxicity). Fludarabine has also been used in combination with mitoxantrone and dexamethasone [17], and it was found that the combination was highly active in a group of 51 relapsed indolent lymphomas, with a CR rate of 47% and PR rate of 47%, although these responses were not durable. This regimen is complicated by a high rate of opportunistic infections and is also administered predominantly by the intravenous route. The present CID regimen may provide an alternative or additional option to the existing second-line regimens.

The novel combination of chlorambucil, dexamethasone and idarubicin in this study was an effective regimen for LGNHL and was associated with minimal toxicity which was not age related. Whether the addition of the anthracycline to the chlorambucil and steroid would result in improved efficacy is at present unknown, but a randomized trial within the SNLG is currently seeking to answer this question. Given that many patients with LGNHL may survive beyond 10 years with this disease it will be some time before the final results of this study will be available.

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