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ORIGINAL ARTICLE

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The development of targeted chemotherapy for CNS lymphoma—a pilot study of the IDARAM regimen

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Abstract *Purpose*: We have developed and evaluated a CNS-targeted chemotherapy regimen based on the pharmacokinetic properties of the individual drugs in the combination. *Patients and methods*: In a twin-track study, 16 patients with secondary CNS lymphoma (SCNSL) and 8 with primary CNS lymphoma (PCNSL) were treated with IDARAM which comprised idarubicin 10 mg/m^2 i.v., days 1 and 2; dexamethasone 100 mg, 12-h infusion, days 1, 2 and 3; cytosine arabinoside (ARA-C) 1.0 g/m^2, 1-h infusion, days 1 and 2; methotrexate 2.0 g/m^2, 6-h infusion, day 3 (with folinic acid rescue); and cytosine arabinoside 70 mg plus methotrexate 12 mg, intrathecally, days 1 and 8. Two cycles were delivered at 3-weekly intervals. After response assessment, patients received adjuvant cranial radiotherapy (40 Gy over 20 fractions). *Results*: The series comprised 24 patients, 11 male and 13 female. Their median age was 53 years (range 21 to 73 years). Grade 4 neutropenia and thrombocytopenia occurred in the majority of patients treated. Of the eight PCNSL patients, seven achieved complete remission (CR). Four remained in CR at the time of this report with a median duration of follow-up of 25 months (range 11 to 42 months). Of the 16 SCNSL patients, 12 achieved CR. Seven patients remained in CR at the time of this report with a median duration of follow-up of 24 months (range 18 to 57 months). *Conclusion*: This study suggests that IDARAM is an effective regimen in both PCNSL and SCNSL and is suitable for further development and evaluation.

Keywords Central nervous system · Chemotherapy · Lymphoma · Radiotherapy

This work is presented on behalf of the Central and Southern Lymphoma Group.

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Introduction

Non-HIV-related primary CNS lymphoma (PCNSL) is rare, accounting for only 1 to 2% of all lymphomas, but is thought to be increasing in incidence [8, 13]. It usually affects deep regions of the brain with multiple foci of activity with meningeal seeding being seen with more advanced disease [11]. Virtually all PCNSL are B-cell malignancies, and initially involve the perivascular stroma before spreading to adjacent white matter. There is no evidence that these tumours are genetically distinct from systemic lymphomas [22].

Secondary CNS lymphoma (SCNSL) may be seen in most of the lymphoproliferative diseases. A high risk of this occurring in particular subtypes, notably lymphoblastic disease and Burkitt's lymphoma, has encouraged specific prophylactic measures. In other aggressive lymphomas a high international prognostic index (IPI) and involvement of more than one extranodal site increases the risk of SCNSL. Lymphomas arising in the testis and breast and where there is bone marrow infiltration have

also been identified as particular associations [12, 13, 19]. Direct invasion may occur when a lymphomatous tumour arises in or involves sites adjacent to the CNS.

In PCNSL radiotherapy has been a principal treatment modality though with appreciable associated morbidity and poor overall outcomes. There is evidence that the addition of chemotherapy can achieve modest improvement in disease-free and overall survival [9, 16]. Regimens such as CHOD/BVAM (cyclophosphamide, doxorubicin, vincristine, dexamethasone/BCNU, vincristine, cytosine arabinoside, methotrexate) have shown promise but evidently do not obviate the need for radiotherapy [2]. There is a clear need to continue to try to optimize chemotherapy regimens and to explore combinations specifically formulated to take account of pharmacokinetic principles of drug delivery to the CNS. The most important problem is the blood-brain barrier. Agents such as methotrexate in high dosage have been used to overcome this, sometimes with attempts to disrupt the barrier by altering osmotic gradients [14]. Most anthracyclines probably do not cross the blood-brain barrier but there is evidence that idarubicin is atypical in this respect. Idarubicinol, the cytotoxic metabolite of idarubicin, is present in the CSF following intravenous administration at sustained levels [18]. Cytosine arabinoside also penetrates to the brain parenchyma and concentrations in the CSF are significantly higher when the infusion time is decreased [7]. The nitrosourea BCNU and dexamethasone will also penetrate the blood-brain barrier [23]. Dexamethasone is lympholytic when given in high doses and often provides immediate symptomatic benefit.

It is clearly necessary to investigate the effectiveness and toxicity of combinations of drugs likely to be effective within the CNS. We carried out a twin-track pilot study of a specifically CNS-targeted combination—idarubicin, dexamethasone, cytosine arabinoside and methotrexate (IDARAM)—in PCNSL and SCNSL.

Patients and methods

Patients

The basis for this study was formulated within the UK Lymphoma Group (as LY09) but it was subsequently undertaken by the Central and Southern Lymphoma Group as CSLG-P10. Between August 1998 and May 2002, 24 patients with CNS lymphoma were enrolled at seven UK centres. Informed consent was required from each patient. Inclusion criteria included: a pathologically confirmed diagnosis of non-Hodgkin's lymphoma (NHL) involving the CNS; age >16 years; normal renal function; and measurable disease. Exclusion criteria included patients who were immunosuppressed secondary to HIV infection or organ transplantation, those with any severe coexisting illness, or exposure to $>400\ mg/m^2$ of anthracycline. Survival was calculated in months from the commencement of IDARAM.

Of the eight patients with PCNSL, three were male and five female with a median age of 54 years (range 38–73 years). All patients were newly diagnosed. In all patients the tumour was diagnosed as diffuse large B-cell NHL according to the REAL (Revised European-American Lymphoma) criteria. Seven patients had mass lesions, which varied in maximum diameter from 2 to 6 cm and were solitary in six patients. In one patient the disease was purely meningeal.

Of 16 patients with SCNSL, 8 were male and 8 female, with a median age of 51 years (range 21–69 years). Nine patients had a mass lesion, varying in maximum diameter from 2 to 5 cm. The CSF was involved in six patients. One patient had diffuse brain stem and cerebellar involvement. The histopathological diagnosis according to the REAL criteria was diffuse large B-cell NHL in 13 patients, follicular NHL in 2, transformed follicular NHL in 1 and primary sclerosing mediastinal B-cell NHL in 1. Two patients had had previous testicular lymphoma and three had had previous breast lymphoma. Nine had disease at other sites above or below the diaphragm on staging. The bone marrow was involved in two patients. Four were early relapses, defined by CNS relapse <6 months after the initiation of therapy for systemic disease.

Table 1 Characteristics of patients with secondary CNS lymphoma, and response data (*DLBL* diffuse large B-cell non-Hodgkin's lymphoma, *PSMBC* primary sclerosing mediastinal B-cell non-Hodgkin's lymphoma, *n/a* not available)

Patient	Age (years)	Sex	Previous therapy[a]	Disease subtype	Time to CNS relapse (months)	IPI	Response	Survival (months)
1	40	F	CHOP	Follicular	<6	3	PD	3
3	58	F	CHOP, FluDAP, IMED	DLBL, breast	>6	1	CR	>20
4	58	M	CHOP	DLBL	<6	4	PD	3
5	49	M	Radiotherapy	DLBL, testicular	>6	2	CR	24
7	35	M	CHOP	DLBL	>6	1	CR	>24
8	56	F	CHOP	DLBL skin, lung	<6	3	CR	3
9	67	M	CHOP	Follicular, bowel	>6	3	CR	>51
13	46	M	CHOP	DLBL, testicular	>6	1	CR	>12
14	57	F	CHOP	DLBL	>6	4	PD	1
16	48	M	CHOP	Transformed follicular	>6	2	CR	9
17	49	F	PMitCEBO	DLBL, breast	>6	3	CR	8
18	53	M	CHOP	DLBL	>6	2	CR	>14
19	42	M	CHOP	DLBL	>6	n/a	CR	>12
21	56	F	CHOP	DLBL breast, thyroid	<6	4	PD	1
22	53	F	CHOP	DLBL	>6	4	CR	>12
23	21	F	CHOP	PSMBC	>6	3	CR	>23

[a]*CHOP*cyclophosphamide, doxorubicin, vincristine, prednisolone; FluDAP fludarabine, doxorubicin, cytosine, cisplatin; *IMED* ifosfamide, mitoxantrone, etoposide, dexamethasone; *PMitCEBO* prednisolone, mitoxantrone, cyclophosphamide, etoposide, bleomycin, vincristine

Table 2 Characteristics of patients with primary CNS lymphoma, and response data

Patient	Age (years)	Sex	IPI	Response	Survival (months)
2	63	M	3	CR	4
6	54	F	0	CR	>31
10	38	F	1	CR	>43
11	54	M	2	PD	2
12	55	M	2	CR	>20
15	73	F	3	CR	>10
20	52	F	1	CR	8
24	66	F	2	CR	>5

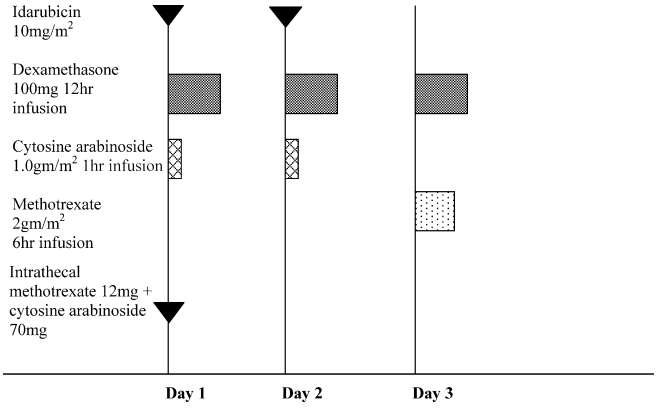

Fig. 1 The IDARAM regimen. GCSF 263 μg is started on day 7 until the neutrophil count is greater than 1.0×10^9/l. Cycles are repeated after 21 days, with two cycles considered as standard therapy

The key patient characteristics of both groups, including IPI category, are shown in Tables 1 and 2 together with previous treatment where relevant; none of the SCNSL patients had received CNS prophylaxis.

Treatment

The IDARAM chemotherapy regimen is shown in Fig. 1. This comprised idarubicin 10 mg/m^2, i.v., days 1 and 2; dexamethasone 100 mg, 12-h infusion, days 1, 2 and 3; cytosine arabinoside (ARA-C) 1.0 g/m^2, 1-h infusion, days 1 and 2; methotrexate 2.0 g/m^2, 6-h infusion, day 3 (with folinic acid rescue); and cytosine arabinoside 70 mg plus methotrexate 12 mg, intrathecally, days 1 and 8 (repeated weekly in patients with meningeal disease to 3 weeks after clearance of abnormal cells in CSF), and granulocyte colony-stimulating factor, lenograstim (Granocyte, Chugai) at 263 μg from day 7 until the neutrophil count reached 1.0×10^9/l. Dose modifications were allowed if there was cytopenia that clearly reflected previous cytotoxic chemotherapy. Cycles were repeated at 3-weekly intervals. Following complete staging after course 2, the protocol was for patients to go on and receive cranial radiotherapy at a dose of 40 Gy over 20 fractions.

Assessment of response

The objectives of the study were to investigate the response and toxicity of at least two courses of IDARAM chemotherapy. The key assessments were made both clinically and radiologically. Response criteria were as follows: complete remission (CR)—resolution of all apparent disease; partial response (PR)—a partial resolution of >50% of assessable disease, determined as the product of two diameters of measurable lesions; minor response/no change (MR/NC)—reduction of <50% in measurable disease but with no disease progression; and progressive disease (PD).

Assessment of toxicity

The toxicity of the regimen was graded according to World Health Organisation criteria.

Results

PCNSL

All patients with PCNSL received the full protocol of two cycles of IDARAM followed by radiotherapy. In one patient with purely localized lumbar meningeal disease, radiotherapy was restricted to 10 Gy to the lumbosacral region. Of the eight PCNSL patients, seven (88%) achieved a CR after two cycles of IDARAM. Only one patient was unresponsive (PD) and died after radiotherapy. Of the seven patients achieving a CR, three (38%) subsequently relapsed after 4, 8 and 21 months, respectively, and the remaining 4 (50%) were in continuing remission at the time of this report with a median duration of follow-up of 25 months (range 11 to 42 months).

SCNSL

Of the 16 patients with SCNSL, 13 received at least two cycles of IDARAM. Three patients received one course due to early death. The cause of death was attributed to progressive CNS lymphoma. Ten patients went on to receive cranial radiotherapy. Six patients did not receive radiotherapy because of early death. One patient underwent four cycles of IDARAM because of labile disease, but still achieved a CR and went on to receive high-dose therapy (HDT) without radiotherapy.

The CR rate for the SCNSL patients was 75% (12 patients). Four patients (25%) had PD. Of the 12 patients showing a CR, five had relapsed at the time of this report. Two patients relapsed and died after 8 and 12 months. One patient who had a neurological CR subsequently developed worsening of disease outside the CNS and died after 9 months. One patient died 24 months after presentation; post mortem examination revealed a pulmonary embolus, but there was microscopic evidence of cerebral lymphoma. One patient relapsed after 15 months and was receiving palliative care at the time of this report. Eight patients (50%) were currently in continuing CR with a median duration of follow-up of 31 months (range 12 to 51 months).

The four SCNSL patients who had relapsed early died within 3 months, whereas the median survival in those patients relapsing after 6 months had not been reached. Two SCNSL patients had received HDT with

Table 3 Toxicity data (one patient was not evaluated due to early death)

Toxicity (WHO criteria)	Number (%) experiencing severe (grade 3/4) toxicity	Number (%) experiencing any toxicity
Haematological	23 (95%)	23 (95%)
Infection	6 (25%)	22 (91%)
Nausea and vomiting	3 (13%)	16 (%)
Gastrointestinal	5 (13%)	16 (67%)
Central neurotoxicity	2 (8%)	1 (4%)
Peripheral neurotoxicity	0	0
Cardiac	0	0
Renal/bladder	0	2

autologous stem cell transplantation as further consolidation. One subsequently relapsed and died and the other was in a continuing remission at the time of this report.

Radiotherapy was delivered after a median of 9 weeks after IDARAM chemotherapy (range 6 to 13 weeks).

Toxicity

The observed toxicities are shown in Table 3. Haematological toxicity following IDARAM was predictable. Grade 3/4 haematological toxicity was seen in 23 patients (95%). Six (25%) had a grade 3/4 infection during neutropenic episodes. Nausea and vomiting was grade 3/4 in three patients (13%). Three patients (13%) developed neurotoxicity. One had an episode of dysphasia that lasted for less than 24 h on the first day of chemotherapy. Two patients developed delayed CNS morbidity after radiotherapy. One patient developed progressive dementia, bladder incontinence and ataxia after 7 months and another developed a deficit in short-term memory after 10 months.

Discussion

The IDARAM regimen was developed as CNS-targeted chemotherapy. The results of this pilot study demonstrate that it can be effective in both PCNSL and SCNSL. In PCNSL seven of the eight patients achieved a CR and in SCNSL the CR rate was 12 out of 16 (75%). These response rates are achievable with predictable toxicity principally reflecting reversible myelosuppression. The planned approach per protocol was to give adjuvant radiotherapy following two courses of "induction" chemotherapy. This study was not primarily designed to investigate longer term outcomes, but four of the seven PCNSL patients who achieved a CR continued in remission with a median duration of follow-up of 25 months. Seven of the SCNSL patients (44%) were in continuing CR with a median follow-up of 24 months.

A standard approach to the treatment of primary cerebral lymphoma is cranial radiotherapy but outcome with this approach is poor and is associated with significant morbidity. Acute encephalopathy may occur in the days or weeks following treatment. Delayed neurotoxicity may occur in up to 80% of patients [15]. This can take the form of global neurocognitive deterioration, brain atrophy and necrosis and is a cause of significant long-term morbidity [16, 20]. Chemotherapeutic approaches are hampered by the blood-brain barrier, which may limit the doses of chemotherapy deliverable into the CNS. Of specific regimens, CHOD/BVAM has been extensively investigated although not all of its constituent drugs reliably cross the blood-brain barrier, disrupted early in the course of the disease enhancing activity. High rates of neurotoxicity have been found with CHOD/BVAM followed by radiotherapy, with 62% of elderly patients developing dementia [2]. In order to reduce these high rates, the dose of radiotherapy was reduced and compared to standard doses. A lower response rate and higher relapse rate in this study in the patients receiving the lower dose of radiotherapy [3].

The BOMES regimen (BCNU, vincristine, methotrexate, etoposide) has yielded response rates of 84% without additional radiotherapy [5]. Vincristine is commonly used in several of the published regimens, yet it has been shown recently that following intravenous bolus injection there is no detectable vincristine in the CNS [10]. This and several other studies have indicated that regimens based on particularly methotrexate and methotrexate plus cytosine arabinoside may yield high response rates, raising the possibility of avoiding the need for early adjuvant radiotherapy [4, 6, 17]. This may be of particular importance in the elderly. We have selected a combination of chemotherapeutic drugs based on their pharmacokinetic properties and dose levels aimed at delivering effective chemotherapy to the CNS. Nitrosoureas are known to penetrate into the CNS but were omitted from our regimen because of the risk of stem cell depletion and our wish to retain the option of HDT. HDT has been investigated previously in CNS lymphoma. CR rates of 36% in refractory/recurrent PCNSL [1, 21] and 41% in SCNSL have been reported. European Bone Marrow Transplant (EBMT) data suggest that results are superior in SCNSL when active CNS disease is not present at the time of transplantation and that the presence of previous CNS lymphoma does not affect overall outcome in relapsed systemic lymphoma, with a 5-year progression-free survival of 42% [24].

Although patients at greater risk of SCNSL may be identifiable, uniform and optimum prophylaxis has not been developed and there is still a clear need for effective chemotherapy regimens. The IDARAM regimen has an acceptable toxicity profile and could be the template for such a regimen. In PCNSL comparison of approaches that incorporate radiotherapy with those that do not will probably require concerted multinational collaboration because of the comparative rarity of cases. In both

PCNSL and SCNSL, the achievement of CR is of prime importance as a first step in improving outcomes. Given the toxicity of radiotherapy to the brain, the development of more effective chemotherapy regimens is clearly of importance. We chose to consolidate responses to two cycles of CNS-targeted chemotherapy with radiotherapy but there would be a case for additional courses of chemotherapy to optimize and consolidate responses, possibly with the addition of other agents such as nitrosoureas with a view to obviating the need for radiotherapy. Such approaches will be the basis for further study.

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