A pilot study of CODOX-M/IVAC in primary refractory or relapsed high-grade non-Hodgkin's lymphoma. A Scotland and Newcastle Lymphoma Group Study

KERRI L. DAVIDSON, MAUREEN B. DEVANEY, JANE E. TIGHE, STEVEN Y. ROGERS, DAVID J. DUNLOP, MICHAEL J. MACKIE, RANJIT V. THOMAS, PETER R.E. JOHNSON

Background and Objectives. The prognosis in patients with primary refractory or relapsed high grade non-Hodgkin's lymphoma (NHL) is very poor — the 5-year survival being generally reported at 10%.

Design and Methods. Multiple salvage regimens have been investigated and, while response rates of 50-80% have been noted in selected patients, the long-term prognosis remains poor. Following the encouraging results in high risk Burkitt's and Burkitt-like lymphoma using the CODOX-M and IVAC protocols, we performed a pilot study using a similar regimen in patients with primary refractory or relapsed high grade NHL.

Results. The regimens were modified by a reduction in the intensity of intrathecal therapy. It was planned to mobilize peripheral blood stem cells following the IVAC cycle for use in subsequent autologous peripheral blood stem cell transplantation in chemosensitive patients. The initial plan was to recruit 50 patients, but the study was closed after 8 due to excessive toxicity.

Interpretation and Conclusions. We conclude that the CODOX-M/IVAC regimen is too toxic for this group of patients and does not result in better response rates than those to currently available salvage regimens.

Key words: high grade NHL, relapse/refractory patients, salvage therapy, CODOX-M/IVAC regimen.

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From the Western General Hospital, Edinburgh (KLD, MBD, MJM, RVT, PREJ); Aberdeen Royal Infirmary, Aberdeen (JET); Victoria Hospital, Kirkcaldy (SYR); Beatson Oncology Center, Glasgow (DJD), United Kingdom.

Correspondence: Dr. Peter R.E. Johnson, Consultant Hematologist, Western General Hospital, Crewe Road, Edinburgh EH4 2XU, UK. E-mail: peter.johnson@luht.scot.nhs.uk

Approximately 50-70% of patients with non-localized high or intermediate grade non-Hodgkin's lymphoma (NHL) will have a complete response to multi-agent chemotherapy. The standard regimen for such patients is cyclophosphamide, doxorubicin, vincristine and prednisolone (the CHOP regimen) as demonstrated by the Southwestern Oncology Group/Eastern Co-operative Oncology Group (SWOG/ECOG) intergroup trial.[1] From 30 to 50% of patients will be cured using such chemotherapy. There does, however, remain a significant percentage of primary refractory patients who do not respond to initial CHOP chemotherapy, and others who relapse after an initial response. The prognosis in these patients is very poor – the 5-year survival being generally reported as approximately 10%.

Multiple salvage regimens have been described, and while response rates of 50-80% in selected patients have been reported, the long-term prognosis remains poor. In patients responding to a salvage regimen, high dose therapy with marrow stem cell support has been shown to improve survival.[2]

The *Scotland and Newcastle Lymphoma Group* (SNLG) recently reported its results from using a standard salvage protocol consisting of ifosfamide, etoposide and epirubicin (IVE) in 56 patients with high-grade NHL (51 diffuse large B-cell, 5 peripheral T-cell). Thirty-eight of these patients (68%) responded – 22 (39%) with a complete remission, 2 (3%) with a good partial remission, and 14 (25%) with a partial remission. Of these 38 responders, 22 relapsed, 15 (39%) within 12 months. The median survival in the responders was 7 months and survival at 36 months was 22% (Taylor *et al*., *1999*, *personal communication*).

In this situation, there is a critical need to identify novel drugs or regimens for patients with primary refractory or relapsed disease. Such regimens need to be sufficiently intensive to induce disease response, but should also be designed to allow stem cell collection with subsequent high dose therapy. In 1996, Magrath *et al*. reported results in patients with Burkitt's and Burkitt-like lymphoma using a highly intensive CODOX-M protocol consisting of cyclophosphamide, doxorubicin, vincristine and methotrexate alternating, in higher risk patients, with an additional regime called IVAC – ifosfamide, etoposide, high dose Ara-C and methotrexate.[3] Of 41 patients (20 adults and 21 children), 7 (5 adults and 2 children) were considered low risk and received CODOX-M alone and 34 (15 adults and 19 children) were considered high risk and received CODOX-M alternating with

IVAC for a total of 4 courses. The event-free survival in all 41 patients was 92% at 2 years.

These encouraging results were confirmed in the United Kingdom Lymphoma Group LY06 study.[4] This was an international, multi-center study using International Prognostic Index-based criteria to assign adults with Burkitt's lymphoma into prognostic groups. Low risk patients (n = 12) were treated with three cycles of modified CODOX-M and high-risk patients (n = 40) received four cycles of alternating modified CODOX-M and IVAC chemotherapy. The overall 2-year event-free survival was 65% and 2-year overall survival was 73%. The short-term toxicity was, however, noted to be severe.

In the light of these encouraging results, albeit in patients with Burkitt's and Burkitt-like lymphoma, we performed a pilot study of the CODOX-M/IVAC regimens in patients with primary refractory or relapsed high grade NHL. Although this is a different histologic subtype of lymphoma, the CODOX-M and IVAC regimens contain drugs of proven benefit in this type of disease. It was also considered that IVAC should be an effective regimen to mobilize peripheral blood stem cells using granulocyte colony-stimulating factor (G-CSF) augmentation.

Design and Methods

Selection and eligibility of patients

Patients between the ages of 16 and 60 with primary refractory or relapsed high-grade NHL were recruited. Eligible histologic subtypes were diffuse large B cell, peripheral T-cell lymphoma (unspecified), angio-immunoblastic T-cell lymphoma, extranodal NK/T-cell lymphoma, enteropathy-type T-cell lymphoma or anaplastic large cell lymphoma (REAL classification).[5] Primary refractory patients were defined as those having a less than 50% reduction in measurable disease following primary therapy (i.e. failure to achieve a complete or partial response), or patients with > 50% disease reduction following primary therapy in whom the treating physician was intending to continue therapy directly with an alternative salvage chemotherapy regimen. Relapsed patients were defined as those in first relapse after initial chemotherapy in whom treatment with a salvage regimen was considered, rather than repeat treatment with the primary regimen. Exclusion criteria were ECOG performance status >2, bilirubin > 2 times the upper limit of normal, creatinine clearance < 50 mL/min, previous autologous transplantation, pregnancy, cardiac ejection fraction of < 40%, known positivity for human immunodeficiency virus and inability to give informed consent. Pre-treatment investigations included: World Health Organization (WHO) performance status; Ann-Arbor staging; full blood count (FBC), blood film and erythrocyte sedimentation rate (ESR); full biochemical profile including urea and electrolytes (U&E), creatinine, liver function, lactate dehydrogenase (LDH) and urate; direct measurement of creatinine clearance; bone marrow aspirate, trephine and immunophenotyping; chest X-ray; computed tomography (CT) scans of chest and abdomen and CT/magnetic resonance imaging (MRI) of the major disease area if not already imaged. In all cases the pathology was reviewed by a histopathologist with a specialized interest in lymphomas. We aimed to recruit 50 patients throughout the Scotland and Newcastle Lymphoma Group. Stopping rules were not defined prior to study initiation.

Treatment schedule

The study protocol was that all patients recruited should receive one cycle of CODOX-M followed by one cycle of IVAC as detailed below. Responding patients were then planned to undergo myeloablative chemotherapy and peripheral blood stem cell (PBSC) transplantation using conditioning with etoposide and melphalan. Those not eligible for transplantation were to receive a further cycle of CODOX-M and IVAC. Post-transplantation radiotherapy to bulky disease sites could be given at the discretion of the treating physician.

A single lumbar puncture with intrathecal cytarabine was administered to all patients on day +1. Cerebro-spinal fluid (CSF) cytospin was performed and if there was no evidence of central nervous system (CNS) lymphoma, no further intrathecal treatment was given. In cases in which CNS disease was documented or strongly suspected, the CODOX-M regimen was adjusted with an addition of intrathecal methotrexate 12.5 mg on day +15 followed by oral folinic acid 15 mg, 24 hours later. The IVAC regimen was modified by addition of intrathecal methotrexate 12.5 mg on day +5 again with oral folinic acid 15 mg, 24 hours later.

As these regimens are highly intensive, patients were admitted for chemotherapy and support of pancytopenia. A Hickman line or peripherally inserted central venous catheter was placed prior to chemotherapy administration. Blood product support, antibiotic treatment, anti-emetics, anti-microbial prophylaxis and use of total parenteral nutrition (TPN) was at the discretion of the treating physician and given in accordance with locally agreed protocols. G-CSF (Lenograstim) use to hasten neutrophil recovery following CODOX-M or non-PBSC mobilizing IVAC, was again at the discretion of the treating physician but when used, was commenced as detailed above. Predsol eyedrops were administered to prevent chemotherapy-induced conjunctivitis during the IVAC cycle. All patients were scheduled to undergo PBSC mobilization after the IVAC course using lenograstim 5 μg/kg subcutaneously once daily from day +7. The criteria for when to harvest stem

Treatment schedule.

CODOX-M regimen

Day	*Drug*	*Dose*	*Route*	*Time*
1	Cyclophosphamide	800 mg/m^2	Intravenous (IV)	
	Vincristine	1.5 mg/m^2 (max 2 mg)	IV	
	Doxorubicin	40 mg/m^2	IV	
	Cytarabine	70 mg	Intrathecal	
2-5	Cyclophosphamide	200 mg/m^2	IV	Daily
8	Vincristine	1.5 mg/m^2 (max 2 mg)	IV	
10	Methotrexate	1200 mg/m^2	IV	Over 1 hour
		240 mg/m^2	IV	Hourly for a total of 24 hours
11	Leucovorin	192 mg/m^2	IV	At 36 hours
		12 mg/m^2	IV	Every 6 hours
13	G-CSF (Lenograstim)	5 µg/kg	Subcutaneous	Daily to neutrophil recovery

IVAC regimen

Day	*Drug*	*Dose*	*Route*	*Time*
1-5	Etoposide	60 mg/m^2	IV	Daily over 1 hour
	Ifosfamide	1500 mg/m^2	IV	Daily over 1 hour
	Mesna	360 mg/m^2 (mixed with ifosfamide)	IV	Over 1 hour
		Then 360 mg/m^2	IV	3 hourly (seven doses/ 24 hour period)
1-2	Cytarabine	2 g/m^2	IV	Over 3 hours, 12 hourly (total 4 doses)
7	G-CSF	5 µg/kg	Subcutaneous	Daily to neutrophil recovery

cells were dependent on the treatment center. The target CD34 cell yield was 5×10^6/kg (minimum 2.5×10^6/kg). Chemotherapy-related toxicity was graded in accordance with the WHO toxicity profile at weekly intervals.

Evaluation of response

The primary study endpoint was response following IVAC. Complete response (CR) was defined as the disappearance of all clinical, radiological and biochemical evidence of disease. A good partial response (GPR) was at least a 75% reduction in tumor mass and partial remission (PR) was at least a 50% decrease in the sum of all the measured mass lesions. Progressive disease (PD) was defined as a measurable progression of disease in at least one site in the absence of response at the other sites during treatment.

Results

The initial plan was to recruit 50 patients, but the study was closed after 8 patients due to excessive toxicity. The median age of the recruited patients was 45 years (range 31-59 years). There were 6 males and 2 females. Five patients had primary refractory NHL and three had relapsed disease. The characteristics of the patients at study entry are shown in Table 1.

All eight patients received CODOX-M as per protocol. Hickman lines were inserted in all patients. Six received prophylactic antibiotics. All patients experienced WHO grade 3/4 granulocyte and platelet toxicity and all required intravenous antibiotics for a median duration of 16 days (range 5-26 days). Seven were given G-CSF following CODOX-M to aid neutrophil recovery. Seven

Table 1. Patients' baseline characteristics prior to salvage chemotherapy.

Case	Age	Sex	Diagnosis	Stage	Primary therapy (n. of cycles)	ECOG performance status	Stage	U&E	LDH (U/L)	FBC Neut (×10⁹/L)	FBC Plt (×10⁹/L)
					Refractory patients						
1	59	M	DLBCL	Refractory	CHOP (6)	2	IVA	N	657	5.3	310
2	44	M	DLBCL	Refractory	CHOP (4)	2	IVB	N	3165	2.3	254
3	39	M	DLBCL	Refractory	CHOP (4)	1	IVB	N	899	0.4	50
4	49	M	DLBCL	Refractory	CHOP (2)	2	IA	N	1302	3.1	376
5	34	M	Ana T	Refractory	CHOP (5)	2	IVB	N	111	1.5	198

Case	Age	Sex	Diagnosis	Stage	Best initial response	Time to relapse (months)	Primary therapy (n. of cycles)	ECOG performance status	Stage	U&E	LDH (u/l)	FBC Neut (×10⁹/L)	FBC Plt (×10⁹/L)
						Relapsed Patients							
6	31	F	MS B cell	Relapsed	PR	3	CHOP (6)	2	II	N	150	5.5	425
7	54	F	DLBCL	Relapsed	CR	84	CHOP (6)	1	IIIB	N	1438	5.8	226
8	50	M	PTCL	Relapsed	CR	9	CHOP (6)	2	IIIB	N	1122	0.8	217

DLBCL: diffuse large B-cell lymphoma; M: male; MSB cell: mediastinal sclerosing B-cell lymphoma; F: female; Ana T: anaplastic T-cell lymphoma; N: normal; PTCL: peripheral T-cell lymphoma; Neut: neutrophil count; CHOP: cyclophosphamide, doxorubicin, vincristine, prednisolone; Plt: platelet count.

Table 2. Hematologic recovery times and hospital stay in days.

Case	Age	Diagnosis	Stage	CODOX-M Neut>0.5 ×10⁹/L	CODOX-M Plt >50 ×10⁹/L	CODOX-M Hospital stay (days)	IVAC Neut>0.5 ×10⁹/L	IVAC Plt >50 ×10⁹/L	IVAC Hospital stay (days)
		Patients' Details		*CODOX-M*			*IVAC*		
1	59	DLBCL	Refractory	25	23	43	16	25	14
2	44	DLBCL	Refractory	Died prior to count recovery (d+34)					
3	39	DLBCL	Refractory	18	19	30	Withdrawn from study		
4	49	DLBCL	Refractory	19	*	19	10	15	20
5	34	Ana T	Refractory	**	**	47	Withdrawn from study		
6	31	MS B cell	Relapsed	21	21	24	14	16	18
7	54	DLBCL	Relapsed	Died prior to count recovery (d+22)					
8	50	PTCL	Relapsed	19	20	20	12	***	14

**Platelet count >100 from day +1; **no count recovery prior to withdrawal from the study; ***platelet count never recovered above 50.*

patients required red cell transfusions, receiving 2-14 units (mean 6 units). Platelets were required in five patients, who received 1-20 units (mean 5.6 units). Two patients required total parenteral nutrition (TPN) for grade 4 stomatitis. Hematologic recovery times and duration of hospitalisation following CODOX-M and IVAC are shown in Table 2.

Two patients died of treatment-related sepsis during the CODOX-M regimen (cases #2 and 7, on day +22 and day +34, respectively). Two were withdrawn from the study after CODOX-M therapy. One had severe neurological toxicity attributed to the chemotherapy (case #3). He subsequently went on to receive DHAP chemotherapy, and is currently alive and in remission from his disease. The other was too frail to continue with further intensive chemotherapy following a prolonged hospital stay of 47 days (case #5); her disease progressed within 2 weeks of cessation and she went on to receive palliative chemotherapy. She died from disease-related complications 179 days following entry into the study.

Four patients received IVAC chemotherapy (cases #1, 4, 6 and 8). All required treatment with intravenous antibiotics, G-CSF to expedite recovery and blood product support. None of the patients required TPN. Three out of the four patients had successful PBSC mobilization. The other failed to produce an adequate stem cell yield off IVAC (case #6). This patient went on to receive a further cycle of CODOX-M. Response assessment after the second cycle of CODOX-M, however, showed disease progression necessitating withdrawal from the study.

In the remaining three patients, disease response was assessed after IVAC and was as follows: 1 good partial response (case #1), 1 partial remission (case #8) and 1 disease progression (case #4). Case 1 went on to receive an autologous transplant with a partial response, which lasted 3 months before progression. He died from his disease at day +359 from study entry.

Discussion

Patients with NHL who fail to respond to first line chemotherapy, or who relapse following a complete response have a poor prognosis. Several salvage chemotherapy regimes have been described, such as cytarabine/platinum-based regimens, e.g. DHAP.[6,7] Ifosfamide has also commonly been used, achieving clinical remission in 29-47% of cases. The responses, however, have not been sustained.[8] More recently various combination chemotherapy regimes with ifosfamide, e.g. IVE, have been reported with improved clinical responses up to 60%.[9] However, prolonged survival benefits have not been seen. Following the success and high cure rates with the CODOX-M/IVAC regimen in patients with similarly aggressive disease, we decided to investigate the use of a similar protocol in patients with relapsed or refractory NHL. The protocol had been used previously in the participating centers in small numbers of patients with Burkitt's and Burkitt-like lymphoma only.

This study was terminated early because of the severe toxicities in the first 8 patients enrolled. In particular, the patients suffered prolonged myelosuppression necessitating intravenous antibiotics and in-patient care for accompanying sepsis, and marked non-hematologic toxicity including mucositis, nausea/vomiting, and severe lassitude. There were two treatment-related deaths during the CODOX-M cycle. This severe short-term toxicity had been recognized previously in the United Kingdom Lymphoma Group LY06 study, although in that study long-term toxicity was not seen. Why our patient group did not tolerate this chemotherapy is not completely apparent. All eight patients were in a high-risk group on the basis of the age-adjusted International Prognostic Index,[10] however, the high-risk Burkitt group did not appear to fare any worse than the low risk group as reported by Magrath *et al*.[3] It is likely that our patients had biologically adverse lymphoma, and their ability to withstand highly intensive regimens had been jeopardized by previous chemotherapy. In this regard, 5/8 had primary refractory disease and the relapsed patients entered the study a short time after their primary treatment.

We conclude that this CODOX-M/IVAC regimen is too toxic for this high-risk group of patients. Whether the regimen may have a role earlier in the therapy of patients identified as having adverse risk disease awaits the results of further trials. At present, such patients should be treated with a currently available salvage regime, followed by consolidation with high dose treatment and peripheral blood stem cell rescue in those with chemosensitive disease. The long-term prognosis in these patients does, however, remain very poor, and efforts to design and test novel therapeutic regimens should continue.

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Pre-publication report

Contributions and Acknowledgments

PREJ: designed study, wrote protocol, recruited collaborators, analyzed data, supervised article preparation, final article approval; KLD: analyzed data, wrote article, final article approval; MBD: supervised study implementation, recruited collaborators, analyzed data, final article approval; JET: collaborated in study design, recruited patients, final article approval; SYR: collaborated in study design, recruited patients, final article approval; DJD: collaborated in study design, recruited patients, final article approval; MJM: collaborated in study design, recruited patients, final article approval; RVT: analyzed data, final article approval.

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