RESEARCH ARTICLE

Fotemustine, Teniposide and Dexamethasone in Treating Patients with CNS Lymphoma

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Abstract

Purpose: We developed and evaluated a regimen including fotemustine, teniposide and dexamethasone (FTD) for treating patients with central nervous system (CNS) lymphoma based on pharmacokinetic properties of individual agents and in combination. Patients and Methods: In a comparison study, 8 patients with primary CNS lymphoma (PCNSL) and 8 with secondary CNS lymphoma (SCNSL) were treated with FTD (comprising fotemustine 100 mg/m2, 1h infusion, day 1; teniposide 60 mg/m2, >0.5 h infusion, on day 2, 3, 4; dexamethasone 40 mg, 1h infusion, on day 1, 2, 3, 4 and 5; and methotrexate 12 mg, cytosine arabinoside 50 mg plus dexamethasone 5 mg intrathecally, on day 2 and 7). Cycles were repeated every 3 weeks. After response assessment, patients received whole brain radiotherapy. Results: Of the 8 PCNSL patients, 4 (50%) achieved CR and 3 (38%) PR, an overall response rate of 88%. Four patients (50%) were in continuing remission at the end of this study after a median follow-up of 30 months (range 10 to 56 months). Of the 8 SCNSL patients the overall response rate was 63% (CR+PR: 38%+25%). All responses were achievable with predictable toxicity mainly reflecting reversible myelosuppression. Conclusion: This study suggests that FTD could be an effective treatment for CNS lymphoma, and is worthy of further evaluation.

Keywords: Central nervous system - lymphoma - chemotherapy

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Introduction

Primary CNS lymphoma (PCNSL) is a rare B-cell variant of non-Hodgkin lymphoma that is confined to the brain, leptomeninges, spinal cord, and eyes. Although PCNSL accounts for less than 7% of brain tumors, its incidence is increasing, particularly in immunocompetent individuals (Miller et al., 1994). By contrast with most primary brain tumors, PCNSL is sensitive to corticosteroids, chemotherapy, and radiotherapy (Detangles et al., 2002; Abrey et al., 2005; Chen et al., 2006). Durable complete responses and long-term survival are possible with these treatments; however, outcome for patients with PCNSL is substantially worse than that for patients with a similar stage of systemic non-Hodgkin lymphoma (Abrey et al., 2000). Therefore, the optimum treatment for patients with PCNSL remains challenging and at present there is no universally accepted therapeutic approach for patients with newly diagnosed disease.

Secondary CNS lymphoma (SCNSL) may be seen in most of the lymphoproliferative diseases. Central nervous system (CNS) involvement in non-Hodgkin lymphoma is a serious, potentially preventable complication that can occur in 5 to 10% of patients (Bierman et al., 2005; Boehme et al., 2007). Its occurrence is directly correlated with pathologic aggressiveness and ranges from less than 3% in the indolent, less-aggressive histologies to as high as 50% in the very aggressive ones such as Burkitt lymphoma (Van Besien et al., 1998). Aggressive treatment once detected can improve neurologic outcome, but because it is often associated with contemporaneous systemic relapse, is rarely associated with long-term survival (Korfel et al., 2011). Despite improvement in the systemic treatment of NHL, effective and tolerable treatment of secondary CNS disease remains a difficult clinical problem.

Although PCNSL is a localized disease, localized treatments have produced discouraging results. Surgery does not appear to have any impact on survival, and doses of radiation that are expected to control non-Hodgkin lymphomas in other sites continue to be associated with high local failure rates (Sutcliffe et al., 1985; Andrés et al., 2011). For patients with proven leptomeningeal disease, intrathecal chemotherapy (usually methotrexate or cytarabine) used to be the standard treatment (McAllister et al., 2000). There is evidence that the addition of chemotherapy can achieve modest improvement in disease-free and overall survival (OBrien et al., 2000; Pels et al., 2003). However, modern combination

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chemotherapy regimens used for the treatment of systemic non-Hodgkin lymphoma have mostly proven ineffective in PCNSL because of the drugs' poor penetration of the CNS and their inability to cross the blood-brain barrier (Mead et al., 2000). 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. Agents such as methotrexate in high dosage have been used to overcome this, sometimes with attempts to disrupt the barrier by altering osmotic gradients (McAllister et al., 2000; Omuro et al., 2007). As high-dose methotrexate can penetrate the CNS, it is an attractive option for the treatment of PCNSL; therefore, other lipophilic drugs that can cross the blood-brain barrier have also been studied. Fotemustine is a CENU with antitumor activity in disseminated melanoma and primary brain tumors in humans. After systemic administration, fotemustine is largely distributed into the central nervous system (Vassal et al., 1998). Teni poside is one of the most commonly used drugs in both primary and secondary malignant brain tumors, and its penetration in normal brain tissue and in brain tumor tissue has been examined widely (Van Tellingen et al., 1997). 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—fotemustine, teniposide and dexamethasone (FTD)—in PCNSL and SCNSL.

Materials and Methods

Patients

Between January 2008 and December 2012, 16 patients with CNS lymphoma were enrolled at the lymphoma center of the First Affiliated Hospital of the Zhengzhou University. Informed consent was required from each patient. Inclusion criteria included: a pathologically confirmed diagnosis of non-Hodgkin' s lymphoma (NHL) involving the CNS; age >12 years; normal renal function; and measurable disease. Exclusion criteria included patients who were immunosuppressed secondary to HIV infection or organ transplantation, neutrophils<1.5/nl, platelets<100/nl, bilirubin elevation, transaminases>3xUNL, creatinine clearance<50 ml/min, acute infection and pregnancy, those with any severe coexisting illness.

Of the eight patients with PCNSL, five were male and three female with a median age of 41 years (range 18-61 years, shown in Table 1). Seven patients were newly diagnosed, and one patient was relapsed after the 6 cycles of HD-MTX single drug treatment. In all patients the tumor was diagnosed as diffuse large B-cell NHL according to the REAL (Revised European-American Lymphoma) criteria. Seven patients had mass lesions, and were solitary in five patients. In one patient the disease was purely meningeal and the CSF was involved in one patient.

Of the eight patients with SCNSL, five were male and three female, with a median age of 37 years (range 12-72 years, shown in Table 2). Six patients had a mass lesion, varying in maximum diameter from 2 to 4 cm. The CSF was involved in three patients. The histopathological diagnosis according to the REAL criteria was diffuse large B-cell NHL in 3 patients, plasmacytoma in 1, precursor T-lymphoblastic lymphoma in 2, precursor B-lymphoblastic lymphoma in 1 and anaplastic large T-cell lymphoma in 1. One patient had previous testicular lymphoma and two had previous breast lymphoma. Five 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. The key patient characteristics of both groups, including PS, CSF and LDH category, are shown in Tables 1 and 2 together with previous treatment which relevant.

Treatment

The FTD chemotherapy regimen is shown in Table 3. This comprised fotemustine 100 mg/m^2, 1h infusion, day 1; teniposide 60 mg/m^2, >0.5 h infusion, day 2, 3, 4; dexamethasone 40 mg, 1h infusion, days 1, 2, 3, 4 and 5; and methotrexate 12 mg, cytosine arabinoside 50 mg plus dexamethasone 5 mg intrathecally, days 2 and 7 (repeated weekly in patients with meningeal disease to 3 weeks after clearance of abnormal cells in CSF), and granulocyte colony-stimulating factor at 300 ug 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. Computed tomography (CT) and magnetic resonance imaging (MRI) were used to determine the extent of the primary lesion, to assess the response after 2 cycles and at the end of the study treatment. Following complete assessment, the protocol was for patients to go on and finally receive whole brain radiotherapy at a dose of 30 Gy over 20 fractions for CR patients or 45 Gy over 20 fractions for not reached CR patients.

Assessment of response and toxicity

The objectives of the study were to investigate the response and toxicity of at least two courses of FTD 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). Progress-free survival (PFS) was calculated from the date of start of FTD therapy to disease progression or relapse, or date of last observation. Overall survival (OS) was determined from the date of start of FTD therapy to death from any cause or the date of last observation. The toxicity of the regimen was graded according to World Health Organisation criteria (Ferreni et al., 2003)

Table 1. Treatment and Outcome of 8 Patients with PCNSL Who Received FTD Chemotherapy

Age/sex	PS	CSF	LDH (U/L)	No. of cycles of FTD	Times of IT(MAD)	Response to FTD	Response to FTD+RT	PFS (months)	OS (months)
56/M	2	N	206	3	6	PR	PR	13	
61/M	2	N	152	4	8	PR	PR	>10	>10
45/F	1	N	193	3	6	CR	CR	>13	>13
25/M	1	P	273	6	12	CR	CR	25	>35
24/M	2	N	287	5	10	NC	NC	9	10
18/M	1	N	202	6	12	CR	CR	>56	>56
42/F	1	N	210	4	8	PR	CR	>40	>40
56/F	3	N	268	5	10	PR	PR	13	14

PS, ECOG scores; CSF, N-negative, P-positive; LDH, normal range from 75 to 245U/L; IT(MAD), intrathecal injection with methotrexate 12 mg, cytosine arabinoside 50 mg plus dexamethasone 5 mg

Table 2. Treatment and Outcome of 8 Patients with SCNSL Who Received FTD Chemotherapy

Age/sex	PS	CSF	LDH (U/L)	Disease subtype	Previous therapy	Time to CNS relapse(months)	No. of cycles of FTD	Times of IT(MAD)	Response to FTD	Response to FTD+RT	PFS (months)	OS (months)
21/M	1	P	216	ALT	CHOP	<6	5	11	CR	CR	7	>9
13/M	3	N	3945	BLB	HyperCAVD	<6	2	3	PD	PD*	2	3
50/F	2	N	223	DLBL	R-CHOP	>6	7	8	CR	CR	19	1
12/M	2	P	167	TLB	BFM-90	<6	4	8	NC	NC	5	6
55/F	2	P	122	DLBL	CHOP+RT	>6	2	4	PR	PR	4	5
72/M	3	N	215	DLBL	R-CHOP+ABVCD	>6	2	4	PR	PR	3	4
31/M	1	N	306	TLB	BFM-90	<6	2	4	NC	NC*	7	9
41/F	2	N	142	PC	VAT+RT	>6	2	4	PR	CR	9	12

ALT, anaplastic large T-cell lymphoma; BLB, precursor B-lymphoblastic lymphoma; DLBL, diffuse large B-cell NHL; TLB, precursor T-lymphoblastic lymphoma; PC, plasmacytoma; RT, radiotherapy. "*", not receive radiotherapy

Table 3. The FTD Regimen

Fotemustine	100 mg/m^2	IV. D1
Teniposide(VM-26)	60 mg/m^2	IV. D2, 3, 4.
Dexamethasone	40 mg/m^2	IV. D1, 2, 3, 4, 5.

MAD, Methotrexate(MTX) 12 mg + Cytosine Arabinoside (Ara-C) 50 mg+Dexamethasone 5 mg, IT., D2, 7. One cycle every 3 wk

Table 4. Toxicity Data

Toxicity (WHO criteria)	Number(%) of severe toxicity (grade3/4)	Number(%) of any toxicity
Haematological	6 (38%)	11 (69%)
Infection	4 (25%)	8 (50%)
Nausea and vomiting	2 (13%)	5 (31%)
Gastrointestinal	3 (19%)	7 (44%)
Central neurotoxicity	0 (0%)	1 (6%)
Peripheral neurotoxicity	1 (6%)	2 (13%)
Cardiac	0 (0%)	0 (0%)
Renal/bladder	0 (0%)	0 (0%)

Results

PCNSL

Overall, 36 cycles of FTD chemotherapy were administered to the 8 patients with PCNSL, with a median of four cycles of FTD per patient (range: 3-6). In addition to the intravenous chemotherapy, all patients received a median of 8 times of intrathecal injection of MAD (range: 6-12). At the completion of chemotherapy, three (38%) achieved a CR and four (50%) got a PR of the eight PCNSL patients. The 3 patients in CR and the 4 patients in PR after chemotherapy were treated with WBRT. No patient interrupted WBRT due to acute toxicity. At the end of the treatment (i.e., chemo-radiotherapy), 4 patients achieved a CR (50%). Only one patient was no changed (NC) and died after radiotherapy. Of the seven patients achieving a CR or PR, three (38%) subsequently relapsed after 13, 13 and 25 months, respectively, and the remaining 4 patients (50%) were in continuing remission at the time of this report with a median duration of follow-up of 30 months (range 10 to 56 months, shown in Table 1).

SCNSL

Of the 8 patients with SCNSL, 26 cycles of FTD chemotherapy were administered to all with a median of three cycles of FTD per patient (range: 2-7). In addition to the intravenous chemotherapy, all patients received a median of 6 times of intrathecal injection of MAD (range: 3-11).

At the completion of chemotherapy, the CR rate for the SCNSL patients was 25% (2 patients) and the PR rate was 38% (3 patients). Two patients (25%) had no change (NC). Only one patient was PD. Six patients went on to receive cranial radiotherapy. At the end of the treatment (i.e., chemo-radiotherapy), 3 patients achieved a CR (38%). Of the five patients showing a CR or PR, all had relapsed at the time of this report. Two patients relapsed and died early within 6 months whereas the median survival in those patients relapsing after 6 months had not been reached. One patient who had a neurological CR then developed the worsening of disease outside the CNS and died after 12 months. One patient died after 21 months because of a pulmonary embolus. One patient relapsed after 7 months and was receiving palliative care at the time of this report. Of the two patients with no change (NC), one relapsed and died within 6 months, and another had changed other therapeutic regimens after 2 cycles of FTD treatment subsequently relapsing after 7

months. One patient who had a PD relapsed and died early within 3 months attributing to progressive CNS lymphoma (shown in Table 2).

Toxicity

The observed toxicities are shown in Table 4. Haematological toxicity following FTD was predictable. Grade 3/4 haematological toxicity was seen in 6 patients (38%). Four (25%) had a grade 3/4 infection during neutropenic episodes. Nausea and vomiting was grade 3/4 in two patients (13%). Three patients (18%) developed neurotoxicity. One had an episode of dysphasia that lasted for less than 24h on the first day of chemotherapy. Two patients developed delayed CNS morbidity after radiotherapy.

Discussion

Lymphoma is a common disease in China (Li et al., 2013; Li et al., 2013; Jin et al., 2014). Primary CNS lymphoma is an extranodal non-Hodhkin's lymphoma that appears pathologically similar to extranodal lymphomas that occur elsewhere in the body, but treatment is different largely because the blood-brain barrier prevents CNS penetration of many cytotoxic drugs. Its outcome remains unsatisfactory if compared with that of patients with extra-CNS lymphomas of a similar stage and histotype, and several factors prevent therapeutic progress. For example, many patients with PCNSL are older at diagnosis, have substantial comorbidities, and have worse performance status than do other groups with systemic non-Hodgkin lymphoma (Hoang-Xuan et al., 2003; Wang et al., 2013; Zhang et al., 2013; Zhang et al., 2013; Zhu et al., 2013). Despite these obstacles, substantial progress has been made. A growing body of evidence from phase II clinical trials has shown the efficacy of several treatment strategies. Results from several studies of high-dose methotrexate have shown improved disease control and longer survival (Obrien et al., 2000; Hoang-Xuan et al., 2003). Effective combination chemotherapy regimens have been developed to incorporate methotrexate and whole-brain radiotherapy (DeAngelis et al., 2002; Batchelor et al., 2003; Wang et al., 2013). Immunotherapy, which revolutionised the treatment of systemic non-Hodgkin lymphoma, also seems to offer benefits for patients with PCNSL. Substantial progress has also been made in the treatment of subpopulations with PCNSL, such as patients with intraocular lymphoma and PCNSL associated with HIV (Rubenstein et al., 2008). However, the optimum treatment for patients with PCNSL remains challenging. Although the standard approach of high-dose methotrixate and whole-brain radiotherapy has resulted in extended survival, the neurological morbidity of this approach remains a significant problem. In particular, elderly patients are at significant risk for progressive neurological decline and dementia. Recent therapeutic strategies have focused on eliminating radiation, particularly in the elderly. Furthermore, patients with reduced renal clearance cannot tolerate high-dose methotrexate because of excessive renal and hepatic toxicity.

The FTD regimen was developed as an attractive new CNS-targeted chemotherapy. The results of this pilot study demonstrate that it can be effective in both PCNSL and SCNSL. In PCNSL, at the completion of chemotherapy, three (38%) achieved a CR and four (50%) got a PR, which got an overall response rate of 88%. At the end of the treatment (i.e., chemo-radiotherapy), four patients achieved a CR (50%). And in SCNSL the overall response rate at the end of the treatment (i.e., chemo-radiotherapy) was 63% (CR+PR: 38%+25%). These response rates are achievable with predictable toxicity principally reflecting reversible myelosuppression. This study was not primarily designed to investigate longer term outcomes, but four of the seven PCNSL patients who got benefit from this regimen continued in remission with a median duration of follow-up of 30 months (range 10 to 56 months).

In this study, 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 supporting our wish to retain the option of Fotemustine. Fotemustine (Muphoran) is an anti-cancer drug from the family of nitrosourea and experimentally it possess a large anti-tumour activity. It has been investigated previously in many brain tumors, but no relevant report in primary or secondary CNS lymphoma. Teniposide was included in our investigations because it is more lipophilic to cross the blood-brain barrier and also is eliminated at a slower rate. It has been shown in clinical trials that metastases to CNS and that primary tumors of the brain respond to teniposide treatment (Muggia et al., 1994).

Our patients had a dramatic response to the FTD treatment in PCNSL better than in SCNSL. The main reasons for that are the different stage and prognosis elements between the primary and the secondary CNS lymphoma. By definition, PCNSL is a stage I disease. The involvement of different CNS areas such as eyes, meninges, and/or cranial nerves, does not imply a more advanced stage with a worse prognosis, whereas the stage and prognosis of systemic non-Hodgkin lymphoma with the involvement of CNS is serious (Ferreri et al., 1996).

Of the PCNSL patients, the response rate was different due to their different characteristics in age, PS, CSF and LDH status. The combination of 5 independent predictors of response and survival, that is, age, PS, serum lactate dehydrogenase level, cerebrospinal fluid protein concentration, and the involvement of deep structures (IELSG [International Extranodal Lymphoma Study Group] prognostic score) (Ferren et al., 2003). Virtually all studies confirm the importance of age and PS. Age and PS are the only two universally accepted prognostic factors. In the past, some investigators suggested that age is a factor influencing therapeutic choice rather than an independent survival indicator (Jellinger et al., 1992), whereas a critical review of 50 published PCNSL series confirmed age as a powerful independent prognostic variable in 676 assessable immunocompetent patients (Reni et al., 1997). In our study, with a median age of 41 years of 8 patients with PCNSL, this group of patients was young comparing to median age of 60 of patients diagnosed with PCNSL which could also be a factor of a

very good ORR in this group. For the treatment of CNS relapse, there are few prospective randomized studies specifically designed to directly compare therapies. Nevertheless, some trends can be discerned. For example, Boehme et al retrospectively assessed the frequency of CNS relapse in elderly (age >60 years) patients with NHL participating in a large, randomized trial (Boehme V et al., 2009). 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 FTD regimen has an acceptable toxicity profile and could be the template for such a regimen.

In conclusion, our study demonstrates that the FTD regimen has significant positive effects on patients with CNS lymphoma. In both PCNSL and SCNSL, the achievement of response rate 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. However, because of the rarity of the disease, the small number of investigated patients has been a limitation, and for a general assessment further prospective researches with a larger number of cases are needed to evaluate the broad efficacy of the FTD regimen for the CNS-targeted chemotherapy. Such approaches will be the basis for further study.

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