bjh short report

Pralatrexate, a novel class of antifol with high affinity for the reduced folate carrier-type 1, produces marked complete and durable remissions in a diversity of chemotherapy refractory cases of T-cell lymphoma

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Summary

T-cell lymphomas (TCLs) are characterised by poor responses to therapy with brief durations of remissions. An early phase study of pralatrexate has demonstrated dramatic activity in patients with relapsed/refractory disease. Of the first 20 lymphoma patients treated, 16 had B-cell lymphoma and four had refractory aggressive TCL. All four patients with TCL achieved a complete remission. Patients with B-cell lymphoma achieved stable disease at best. For each TCL patient, the response was more durable than their best response with chemotherapy. This early experience is the first to document this unique activity of pralatrexate in TCL.

Keywords: pralatrexate, T-cell lymphoma, antifolate, reduced folate carrier.

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Based on the most recent surveillance epidemiology and end results registry data (Morton *et al*, 2005), it is estimated that there are 114 548 cases of lymphoid neoplasms per year in the United States, of which 87 666 (about 76%) are B-cell lymphoid neoplasms and 10 042 are Hodgkin lymphoma. Only 5–6% of lymphoid malignancies (6228 cases per year) are T/natural killer (NK) cell neoplasms. A series of other studies have found T-cell lymphomas (TCLs) to constitute a small fraction of total non-Hodgkin lymphomas (NHLs) in the US, with reports typically ranging from 10 to 15% (Devesa & Fears, 1992)

In general, TCLs carry a worse prognosis than B-cell lymphomas. In a retrospective analysis of sequential Groupe d'Etudes des Lymphomes de l'Adulte trials for aggressive lymphomas (Gisselbrecht *et al*, 1998), the 5-year survival rate for patients with 1, 2 or 3 risk factors with B- *versus* TCL was 63% vs. 60%, 53% vs. 36% and 35% vs. 23% respectively. Similar adverse results for TCL were also observed for the rate of complete remission (CR). Furthermore, the International Lymphoma Study Group classification project found that peripheral TCL (PTCL) and precursor T-lymphoblastic leukaemia/lymphoma (T-ALL) had some of the worst outcomes of any subtype of lymphoma, with a 5-year survival rate of 26% following treatment with standard doxorubicin containing regimens (Rudiger *et al*, 2002). There are indolent subtypes of TCL, such as mycosis fungoides and primary cutaneous anaplastic large cell lymphoma (ALCL), which do not follow this universally poor prognosis. Among the aggressive TCLs,

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one subtype, ALK-1 expressing systemic ALCL, exhibits an excellent prognosis with a 5-year overall survival in excess of 70% following appropriate therapy. However, these subtypes are the exceptions and represent a minority of cases. Meanwhile, the poor prognosis for the majority serves to underscore the urgent need for new therapies.

The 10-deazaaminopterins are a class of folate analogues that demonstrate greater anti-tumour effects than methotrexate (MTX) against murine tumour models and human tumour xenografts in immunocompromised mice (Sirotnak *et al*, 1984a; Wang *et al*, 2003; O'Connor, 2005; Toner *et al*, 2006). The improved activity is because of the more effective internalisation by the 1-carbon, reduced folate transporter (RFC-1) and the subsequent accumulation in tumour cells through the formation of polyglutamylated metabolites (Sirotnak *et al*, 1984b, 1998). The reduced folate carrier is a foetal oncoprotein that is almost exclusively expressed on foetal and malignant tissue, and is felt to be the principal means through which pralatrexate, although not necessarily other anti-folates, enters the cell. This carrier protein has evolved to efficiently transport reduced natural folates into highly proliferative cells, in order to meet the demands for purine and pyrimidine nucelotides during DNA synthesis. For example, the V_{max}/K_m for pralatrexate is more favourable than for MTX, being incorporated at a rate nearly 14 times greater than that appreciated for MTX. Similarly, the V_{max}/K_m for the folylpolyglutamyl synthetase (FPGS)-mediated glutamylation reactions suggests that pralatrexate is also 10 times more efficiently polyglutamylated compared with MTX. These biochemical features suggest that pralatrexate should be a more potent antineoplastic agent in comparison with MTX, an observation corroborated in several preclinical models of lymphoma, where pralatrexate has been shown to be markedly superior to MTX (Sirotnak *et al*, 1984b, 1998). This initial report describes the marked activity of pralatrexate in TCL.

Patients and Methods

An Institutional Review Board-approved phase I/II study of pralatrexate in patients with relapsed and refractory NHL and Hodgkin lymphoma began in May 2002. All patients provided informed consent. Based on a phase I experience in patients with non-small cell lung cancer (NSCLC), the initial phase II study of pralatrexate in lymphoma employed a dose of 135 mg/m^2 administered as an IV bolus over 3–5 min, every other week. A total of 16 patients were enrolled on this study, including 15 patients with B-cell lymphoma, and one with a PTCL not otherwise specified (PTCL NOS). At this dose, pralatrexate was associated with significant grade 3 and 4 stomatitis, which was markedly greater than that appreciated in the prior NSCLC studies (Krug *et al*, 2000, 2003). Using population-based pharmacokinetic and pharmacodynamic analyses, this toxicity was found to correlate with pralatrexate exposure, and the pretreatment homocysteine (Hcy) and methylmalonic acid (MMA) levels, and could be significantly reduced, if the Hcy and MMA were corrected by supplementation with folic acid and vitamin B12. Based on the observed toxicity, the study was amended to a phase 1/2 study. In the phase I portion of the study, pralatrexate was dosed as follows: 30 mg/m^2 weekly × 3 weeks of a 4-week cycle; 30 mg/m^2 weekly × 6 weeks of a 7-week cycle, then increased by increments of 15 mg/m^2 weekly × 6 weeks of a 7-week cycle. Dose limiting toxicity was seen at 45 mg/m^2 and thus 30 mg/m^2 weekly × 6 weeks for every 7-week cycle was chosen as the maximum tolerated dose. Patients were re-staged every two cycles by computed tomography (CT) scan, and in many cases fluorodeoxyglucose positron emission tomography (FDG-PET) was used to compliment the CT scan information. In some cases, biopsies were performed to establish pathological CR.

Results and discussion

To date, 20 patients have adequate follow-up to be fully evaluated. Striking CRs have been seen among the four patients with TCL (Table I).

The four patients reported here, all had aggressive TCLs that had either relapsed or were refractory to chemotherapy. Patient 1 was a 48-year-old man with PTCL NOS refractory to CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) and ICE (ifosfamide, carboplatin, etoposide) treated on the original phase 2 study at a dose of 135 mg/m^2 every other week. He received only one dose of pralatrexate. As a consequence of this response to therapy, he developed ulceration of his skin lesions, which became infected leading to bacteraemia, precluding additional therapy on study. The skin ulcerations resolved, and a re-staging CT and FDG-PET revealed a PET-negative CR that lasted for 3 months (Fig 1). He was subsequently treated with doxil with no response. Patient 2 was a 65-year-old woman with T-ALL who had been treated with the L-20 regimen, who relapsed 10 months after completing a maintenance MTX program. She experienced a rapid reduction in her disease in the first 2 weeks of pralatrexate, receiving 30 mg/m^2 weekly × 3 weeks. Restaging with CT, FDG-PET and bone marrow biopsy showed complete resolution of radiographical abnormalities and a complete response in the bone marrow by morphology. She maintained this remission on therapy for nearly 12 months, before developing progressive disease. Patient 3 was a 38-year-old man with human T-cell lymphotropic virus-1-associated ATLL who relapsed in the skin and lymph node on maintenance interferon-α and combivir after having achieved a complete response to EPOCH (cyclophosphamide, doxorubicin, vincristine, prednisone etoposide). He was also treated on the phase 1 at 30 mg/m^2 weekly × 3 weeks and attained a clinical CR within the first cycle, which was documented subsequently by CT and FDG-PET. He remains well in continuing CR at 21 months. Patient 4 was a 25-year-old man with γ,δ-expressing subcutaneous panniculitis-like TCL, who was refractory to his previous four chemotherapy regimens, including MTX. He was treated with pralatrexate at the second dose cohort,

Table I. Summary of the demographic information and prior treatments of the T-cell lymphoma patients treated with pralatrexate.

Patients	Patient #1	Patient #2	Patient #3	Patient #4
Age (years)/ gender)	(48) Male	65/Female	38 Male	25 Male
Diagnosis	PTCL NOS	T-cell ALL	HTLV-1 ATLL	γ,δ-Panniculitic T-cell NHL
Date of diagnosis	June 2006	January 2002	October 2003	May 2002
Prior therapy	1. CHOP × 4 cycles (7/02–11/02–Refractory). 2. ICE × 2(12/02–refractory). 3. Campath (3/03).	1. L20-combination chemotherapy. 2. MTX Maintenance × 19 months (5/02–2/04).	1. EPOCH (10/03–2/04). 2. IFNα and combivir (2/04–1/05).	1. Ontak (9/02–11/02). 2. Targretin/IFNα (1/03–10/03). 3. CHOP (4/04–6/04). 4. ICE (6/04). 5. CTX/Pent (7/04–8/04). 6. Targretin/MTX (9/04–2/05)
Pralatrexate dose	135 mg/m^2×1 dose (6/03)	30 mg/m^2 weekly × 3 weeks (×12 cycles; 12/04–11/05)	30 mg/m^2 weekly × 6 weeks (17 cycles; 2/05–6/06)	30 mg/m^2 weekly × 6 weeks (7 cycles; 3/05–1/06)
Response	PET Negative after one dose. Clinical resolution of skin disease.	CR by PET and CT scan. Bone marrow CR (33% at start of treatment).	CR by CT and PET	CR by CT and PET negative. Site of previously documented ulcerated disease pathologically negative.
Duration of response	3 months (off pralatrexate)	12 months (POD on pralatrexate)	16+ months (on pralatrexate)	9 months (POD on pralatrexate)

ALL, acute lymphoblastic leukaemia/lymphoma; ATLL, HTLV-1 associated adult T-cell leukaemia/lymphoma; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; CTX, cyclophosphamide; EPOCH, cyclophosphamide, doxorubicin, vincristine, prednisone etoposide; ICE, ifosphamide, carboplatin, etoposide; IFNα, interferon alpha; POD, progression of disease; PTCL NOS, peripheral T-cell lymphoma, not otherwise specified.

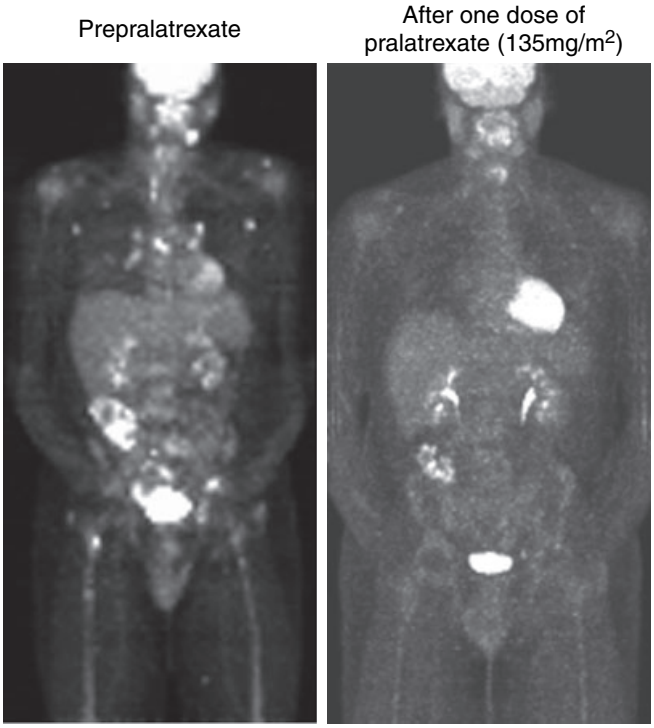

Fig 1. Positron emission tomography-negative complete remission (CR) in a 48-year-old male with refractory peripheral T-cell lymphoma with CR following pralatrexate at 135 mg/m^2×1 dose.

receiving 30 mg/m^2 weekly × 6 weeks. He also achieved a CR documented by CT, PET and biopsy. Interestingly, the natural history of his lesions evolved into a gradual eruption of the subcutaneous lesions to the point where they appeared like circular areas of skin abrasion, followed by resolution of the lesion and abrasion. His CR allowed a muscle graft repair of

one large non-healing, ulcerated lesion that was required prior to allogeneic stem cell transplantation. Following periods of time off-therapy for reconstructive surgery, his disease relapsed after 9 months. In all these cases the drug was well tolerated. There was minimal to no stomatitis with vitamin supplementation, and typically only grade 1–2 thrombocytopenia (which was the dose-limiting toxicity in the weekly phase 1 dose escalation study). Some patients exhibited mildly impaired wound healing while on pralatrexate.

The basis for high-level activity in T-cell malignancies is unexplained and is the subject of further investigation. Obviously, differences in RFC-1 expression between T- and B-cells could explain some of these observations. Despite the fact all patients had different subtypes of TCLs with a different natural history, all four achieved CR, with responses exceeding the patients' best response to combination chemotherapy. Potential comparisons with high-dose (HD) MTX have been raised, but, given that the affinity of pralatrexate for the transporter is at least a log-fold better than for MTX, it is conceivable that pralatrexate may represent a novel means to circumvent the toxicity of HD MTX. Future studies are focused on enhancing accrual, conducting complete pharmacokinetic analyses, and determining the mechanistic basis for these differences between B- and TCL. The ongoing phase 2 study will clarify the importance of vitamin supplementation and nutritional co-variates in a larger patient population. Clearly, additional studies in TCL are warranted.

Author Contributions:

Owen O'Connor designed study, accrued patients, analysed data, wrote manuscript Paul Hamlin designed study, accrued patients analysed data, reviewed paper Carol Portlock accrued patients, edited paper Craig Moskowitz accrued patients and edited paper Ariela Noy accrued patients and edited paper David Straus accrued patients and edited paper Barbara MacGregor-Cortelli helped take of patients on study, edited paper Ellen Neylon analysed data Jennifer Pappanicolu helped take care of patients on study, and edited paper Debra Sarasohn analysed data and edited paper Otila Dumetrescu analysed data and edited paper Diane Mould analysed data and edited paper Martin Fleisher analysed data, contributed to study design and edited paper Andrew Zelenetz contributed to study design, accrued patients and edited paper Frank Sirotnak contributed to data analysis, edited paper Steve Horwitz accrued patients, analysed data, contributed to design and edited paper.

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