Protocol for the use of Zidovudine and Interferon-alpha in the management of Acute Adult T-cell Leukaemia/Lymphoma (ATLL)

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Background

Historical and recent data illustrate the very poor prognosis of acute ATL treated with chemotherapy alone with identical median survival of 6 months from large retrospective case series' published in 1991, 2010 and 2015 (1; 2; 3).

Whilst chemotherapy is widely regarded as the traditional first line therapy for acute and lymphoma ATL, recent data indicate the essential role of zidovudine plus interferon-α (ZDV/IFN) in improving response rates and survival. A recent international meta-analysis identified that patients treated with ZDV/IFN-α alone had similar complete response rates (35%) to those treated with chemotherapy alone (25%). However, the 5 year survival in acute ATL increased from10% if given chemotherapy (with or without maintenance ZDV/IFN-α) to 28% if given ZDV/IFN-α alone. Furthermore, in acute ATL, achievement of CR with anti-viral therapy resulted in significantly improved survival (5 year OS 82%) compared with those not achieving CR (5-year OS 12%) (2).

UK data comparing outcomes in aggressive (acute leukaemic or lymphoma) ATL treated with CHOP alone or supplemented with ZDV/IFN demonstrate the importance of the latter with the use of ZDV/IFN at any time associated with improved survival: no patient survived 5 years with chemotherapy alone compared with 26% 5 year survival for patients treated with CHOP plus ZDV/IFN. In this study no patients with aggressive ATL received ZDV/IFN alone as first line therapy (3). Whilst both studies point to the importance of the ZDV/IFN combination, there are also important differences with the UK study: demonstrating improved response rates and survival with the additional of ZDV/IFN to CHOP for the treatment of lymphoma; improved survival of CHOP/ZDV/IFN in acute ATL compared with CHOP alone; using lower doses of ZDV/IFN than previously recommended. There are no current specific criteria to define 'bulky acute' disease but it is recommended that patients regarded as having significant nodal disease should be managed as per lymphoma subtype.

The mechanism of action of ZDV/IFN-α is largely unknown but is not thought to be truly antiviral. The kinetics of the response to treatment suggests that the mechanism of action is not directly related to apoptotic pathways [10]. As with other tumours, HTLV-1 infected cells show increased telomerase activity resulting in elongated telomeres and failure of replicative senescence [5]. It has been reported that ZDV results in telomere attrition and reactivation of *p53* transcriptional activities leading to senescence of tumour cells [5]. In one study ATL patients responded to treatment only when *p53* was wild type in sequence and conversely, *p53* mutations have been shown to arise at disease relapse or absence of response to treatment, indicating that *p53* may be a predictive biomarker for response to ZDV based treatment[5,6]. Ex vivo and in vitro models of HTLV-1 infection have shown that IFN-α may reduce HTLV-1 gene expression and in co-operation with ZDV activate *p53*[7].

In summary:

ZDV/IFN alone should be regarded as the initial treatment for acute ATL (but not where associated with bulky lymphadenopathy, where benefit has not been demonstrated). It is anticipated that ~1/3 patients should respond, and that non-responders can be switched to chemotherapy. All patients should be discussed and considered for suitable clinical trials.

In this protocol we provide information on dosing, toxicity and assessment of response

***The HTLV-1 request form for molecular diagnostics (proviral load, clonality analysis) is attached to the end of this protocol**

Regimen

Initial therapy
Zidovudine 500mg bd po (may be given IV if clinically required, infused 500mg bd over 4 hours) plus **Interferon-α 9 MU sc daily**

(Roferon-A (IFN-α-2a) is easiest to use as it is available in 3MU, 4.5MU 6 MU and 9MU/0.5ml pre-fill syringes and as an 18MU (0.6ml) cartridge for use in a pen device. It is licensed for the use in AIDS-related Kaposi's sarcoma, hairy cell leukaemia, chronic myelogenous leukaemia, advanced renal cell carcinoma, progressive cutaneous T-cell lymphoma, chronic hepatitis B and chronic hepatitis C, follicular non-Hodgkin's lymphoma, adjunct to surgery in malignant melanoma

Paracetamol 1g 30 minutes prior to Interferon may be required in first two weeks Dose may be better tolerated in the evening

Assessment
Baseline investigations
FBC, white cell differential and blood film with % abnormal lymphocytes and description of appearance (flower cells, convoluted etc).
Biochemistry (U+Es, LFTs, Bone profile, LDH and β2microglobulin)
Serology – HTLV-1, HIV, HCV, HBV (Hep c Ab, Hep s Ag), Strongyloides
Bone marrow biopsy.
Flow cytometry – to include CD3, CD4, CD8, CD25, CD7 expression and CD30, CCR4 where feasible
Lymph node/skin/trephine for histology – to include CD3, CD4, CD8, CD25, CD7, MUM1 expression and CD30, CCR4 where feasible
HTLV-I DNA PCR (Proviral load, PVL) and HTLV clonality in peripheral blood* *(send EDTA to NCHR, request form at end of this protocol).*
If tumour is lymph node or skin, also send tissue block or shavings from block for PVL and HTLV clonality
FISH for TP53 deletion and TP 53 mutational analysis where available
T-cell receptor gene rearrangement in blood or tissue block
PET-CT (if no PET-CT available, for full body contrast enhanced CT scan)
ECHO & troponin if PET suggests cardiac involvement [9]
Lumbar puncture for morphological examination and flow cytometry with intrathecal methotrexate
G6PD level (high risk populations)
Class 1 & 2 HLA typing if likely allogeneic transplant candidate

Routine Monitoring of therapy (first 28 days)

- Outpatients should be reviewed ~daily for first 2 weeks to ensure FBC responding, calcium and electrolytes controlled. HTLV-1 PVL should be sent weekly.
- Patients should continue with treatment for 4-14 days before determining disease progression/failure. Progressive disease may be observed in the peripheral blood during the first 4 days following the start of treatment and

should not be regarded as treatment failure. By day 14 responsive patients should obtain a ~ PR in the peripheral blood and reduction in HTLV PVL. Non-responders (SD/PD) at 14 days should have treatment stopped and switched to standard chemotherapy protocols.

- Frequency of visits may be reduced after initial 2 weeks. Patients should continue on high dose for at least 4-6 weeks or until CR established before dose reductions. Discuss with NCHR
- Patients with CNS involvement at presentation should be treated with concurrent high dose IV methotrexate (patients will require Cr Clearance)

Assessment of Response (at 4 weeks)

Clinical assessment including FBC, film, Calcium, LDH
HTLV PVL and clonality
Flow cytometry
FISH for TP53 deletion or TP 53 mutational analysis (if present at diagnosis)
T-cell receptor gene rearrangement (if present in peripheral blood at diagnosis)
PET-CT (or contrast enhanced CT scan if not available)
Bone marrow biopsy (if involved at presentation)

Evaluation of Response

Complete Remission (CR): No evidence of lymphoma or leukaemia for at least 1 month: Complete disappearance of abnormal clinical and radiological features at presentation, normal calcium, LDH and fewer than 8% abnormal lymphocytes on blood film [8].

Partial Response (PR): Less than 50% residual disease (but not complete remission) and normal serum calcium maintained for at least 1 month.

Stable disease: reduction in WBC or measurable tumours of less than 50% after 1 month.

Progressive disease: 20% increase in measurable disease or number of circulating leukaemic cells.

Dose adjustment at 28 days
CR/PR - The regimen should be continued indefinitely for as long as CR or PR is maintained and blood counts tolerate. No dose reductions for first 4-6 weeks.

SD: Patients with SD at 28 days should be on maximum dosing of ZDV/IFN-α. If on maximum dosing or treatment not tolerated, treatment should be stopped and switched to alternative chemotherapy protocols.

Side Effects

Zidovudine is most commonly associated with:
Nausea +/- vomiting and headache (usually mild and self-limiting)
Macrocytosis (no intervention required)
Nail pigmentation (reversible on stopping therapy)
Skin darkening (reversible on stopping therapy)
Haematological toxicity
Hepatotoxicity
Polymyopathy – more common at this higher dose with long term therapy
Lactic acidosis – rare. Maintain a high index of suspicion
Lipodystrophy – after several months - years on treatment

Interferon-α side effects are dose related:
Most commonly flu' like symptoms (transient)
Fatigue
Anorexia
Nausea and vomiting
Cardiovascular toxicity (very rare but may occur in patients with pre-existing cardiovascular disease or prior cardiotoxic therapy e.g. anthracycline based chemotherapy).
Depression (including suicidal behaviour) has been reported.
Myelosuppression
Hypertrigylceridaemia – monitor lipids
Other reported side-effects include:

- Ocular side-effects.
- Alopecia,
- Hypersensitivity reactions
- Thyroid abnormalities
- Hyperglycaemia
- Psoriasiform rash
- Confusion
- Coma
- Seizures with high dose in the elderly
- Renal failure
- Hyponatraemia

Management of toxicity

Haematological
Neutropenia: Supportive therapy with G-CSF may be necessary if grade 3-4 neutropenia occurs.
G-CSF (Lenograstim 33.6 million units; 263µg / Filgrastim 30 million units; 300µg) given 1-2 times weekly (rather than daily) as required to allow continuation of full dose therapy.
Ideally anti-viral therapy should not be interrupted in the first 4 weeks.

Thrombocytopenia: Discontinue both drugs if grade 4 thrombocytopenia (platelets below 25 x 10^9/L) unless this is due to bone marrow infiltration by ATL. Recommence therapy at 50% reduction in Zidovudine dose when platelets > 75 x 10^9/L (Zidovudine 250mg bd, Interferon-? 6MU/day).

Grade	0	1	2	3	4
WCC	≥4	3.0 – 3.9	2.0 – 2.9	1.0 – 1.9	<1.0
Platelets	Normal	75 < N	50 <75	25 <50	<25
Hb g/dl	Normal	10 < N	8.0 < 10	6.5 < 8.0	<6.5
Neuts	≥2	1.5 < 2.0	1.0 < 1.5	0.5 <1.0	<0.5
Lymphs	≥2	1.5 < 2.0	1.0 < 1.5	0.5 <1.0	<0.5

Non-Haematological

Withhold both drugs if Grade 3 or 4 non haematological toxicity observed
Numbers relate to multiples of upper limit of normal range (ULN)

Liver

Grade	0	1	2	3	4
Bilirubin	Normal	----------	1.0 < 1.5	1.5 < 3.0	>3.0
ALT/AST	Normal	1.0 < 2.5	2.5 < 5.0	5.0 <20	>20
Alk Phos	Normal	1.0 < 2.5	2.5 < 5.0	5.0 <20	>20
Clinical	Baseline	----------	----------	Pre-coma	Hepatic Coma

Flu' like

Grade	0	1	2	3	4
Fever °C*	None	37.1 – 38	38.1 – 40	>40	>40 for 24hr
Chills	None	Mild or brief	Pronounced or prolonged		
Myalgia/ arthralgia	None	Mild	Decreased ability to move	Disabled	
Sweats	None	Mild or occasional	Frequent of drenching		
Malaise	None	Mild, able to continue NDA	Impaired	Bed or chair ridden or unable to care self <50% of waking hours	Bed-ridden or unable to care for self >50% of waking hours
Flu'like	None	Mild	Moderate	Severe	Life-threatening

Opportunistic infection prophylaxis

Pneumocysitis prophylaxis:
Co-trimoxazole 480mg daily or 960mg tiw

Alternatives are **Dapsone 100mg daily** (if G6PD level normal), **Pentamidine** 300mg by nebulised inhalation preceded by Salbutamol 2.5mg monthly or **Atovaquone** 750mg bd.

HSV-1,2, VZV prophylaxis:
Aciclovir 400mg bd

Fungal – Cryptococcus and candida:
Fluconazole 50mg od

Strongyloides stercoralis:
See separate Trust 2016 protocol "Strongyloides stercoralis : Protocol for treatment in patients with Human T-lymphotropic
virus type 1 (HTLV-1)"
2016 recommendation for asymptomatic immunocompromised patients with positive strongyloides serology: Ivermectin ~200mcg/Kg on days 1, 2, 15, 16.

CMV: Patients with evidence of previous CMV infection (CMV IgG detected) should have CMV DNA monitored and treated as required.

Imperial College London

MDU
Molecular Diagnostics Unit

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E-mail: mdu@imperial.ac.uk

Suitable Samples: Whole EDTA blood, CSF to arrive at MDU within 24 hours of venesection/lumbar puncture. Cutaneous, lymph node or tissue biopsy – tissue block or histology slide. Extracted DNA. Do not send plasma. If requesting CSF HTLV-1 DNA viral load send sample EDTA whole blood obtained at the same time point. DX 309701 PADDINGTON 92W

PATIENT INFORMATION

Patient ID number_____

Surname_____

Forename_____

Sex: ☐ male ☐ female

ETHNIC GROUP

☐ White ☐ Indian/Pakistani/Bangladeshi

☐ Black Caribbean ☐ Black African ☐ Black other

☐ Chinese ☐ Japanese

☐ Other/Mixed ☐ Unknown ☐ Not disclosed

SAMPLE INFORMATION

Sample type ☐ ETDA whole blood ☐ CSF

Other (*please specify*)

_____

Date Obtained: _____

TESTS REQUESTED

☐ HTLV proviral qPCR

☐ HTLV typing by PCR

☐ HTLV clonality analysis

CLINICAL/EPIDEMIOLOGICAL INFORMATION

REASON FOR REQUEST:
☐ Clinical investigation

☐ Organ/BM donor
☐ Contact of HTLV+
☐ Stem cell harvest
☐ Milk donor
☐ Blood donor
☐ Needle stick
☐ Other (please specify):

DIAGNOSIS:
☐ Asymptomatic
☐ HAM/TSP
☐ Other neurological symptoms : _____
☐ ATLL - Leukaemia
☐ ATLL - Lymphoma
☐ Other malignancy
☐ HIV co-infected
☐ Uveitis
☐ *S. stercoralis* infection
☐ Polymyositis
☐ Polyarthritis
☐ Alveolitis
☐ Thyroiditis
☐ Bronchiectasis
☐ Hepatitis
☐ Sjögren's syndrome
☐ Other (please specify):

_____

SENDER INFORMATION

Sender name and address

Signature

Postcode_____

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