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"Antivirals" in the Treatment of Adult T Cell Leukaemia– Lymphoma (ATLL)

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Abstract Adult T cell leukaemia / lymphoma (ATLL) is a mature (post thymic) T cell lymphoma caused by the human T-lymphotropic virus type 1 (HTLV-1) infection. Overall survival in the aggressive subtypes (Acute Leukaemia and Lymphomatous) remains poor in part due to chemotherapy resistance. To improve treatment outcome for de novo disease, better induction therapies are required and since the pathogenic agent is known it would seem sensible to target the virus. In a recent meta-analysis the use of zidovudine and interferon alpha (ZDV/IFN) has been associated with improved response rates and prolonged overall survival in leukemic subtypes of ATLL (both acute and Chronic) confirmed in a multivariate analysis. In a more recent UK study the overall response rate for patients with aggressive ATLL treated with chemotherapy alone was 49 % compared to 81 % with combined first line therapy (chemotherapy with concurrent or sequential ZDV/IFN). Combined first line therapy prolonged median OS in acute (p=0.0081) and lymphomatous ATLL (p=0.001).These data support the use of low dose ZDV/IFN with chemotherapy as first line treatment for patients with newly diagnosed aggressive ATLL. Although the mechanisms of action are incompletely understood, some possible explanations for their efficacy will be discussed.

Keywords Antiviral Therapy (AVT) · Adult T cell Leukaemia- Lymphoma (ATLL)

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Introduction

Adult T-cell leukaemia/lymphoma (ATLL) is a malignancy of mature peripheral T lymphocytes caused by the human T cell lymphotropic virus type-1 (HTLV-1). The disease was first described as a clinical entity in 1977 in Japan, with geographical clusters raising the possibility that an environmental or transmissible agent might be implicated in pathogenesis. Following the discovery of human T Cell growth factor (IL-2) permitting long term culture of human T Cells [1] and the refinement of assays to detect reverse transcriptase, a retrovirus was isolated from the lymphocytes of a North American patient with cutaneous T cell lymphoma [2]. Parallel studies in Japan led to the detection of a retrovirus from patients with ATLL nominated the adult T-cell leukaemia virus (ATLV) [3]. Genetic analysis demonstrated the single identity of these viruses which were eventually classified as HTLV-1 and confirmed to be the causative agent of ATLL [4]. HTLV-1 is spread through bodily fluids containing infected cells, most often from mother to child through breast milk, sexual intercourse mainly from men to women or via blood transfusion containing lymphocytes. The lifetime risk of developing ATLL after a long latency period is 2–7 % [4–7].

Presentation of ATLL

ATLL is diagnosed by the characteristic CD4+ CD25+ phenotype of the malignant lymphocyte, the presence of HTLV-1 antibodies in sera and confirmation of HTLV-1 proviral integration in the leukaemic cells or lymphoma. Despite these identifying features the presentations and course of ATLL are diverse. The Japanese Lymphoma Study Group defined four subtypes [8•]: the smouldering ,chronic and acute leukaemic forms and a pure lymphomatous type; the latter two are conveniently referred to as aggressive

ATLL based on the 6–8 month survival. Overall survival in patients with smouldering or chronic ATLL is measured in years. A case can also been made for a 5th subtype, cutaneous ATLL, which differs in presentation, course and preferred treatment [9].The classification has helped clinically to distinguish ATLL from other forms of T cell leukaemia and lymphomas.

Pathogenesis

The main tropism of HTLV-1 is for CD4+ T cells although CD8+ T-cell infection in vivo is observed. In the majority of infected individuals only 0.05–5 % of their T cell compartment is infected and this rate usually persists for decades [10]. Only 10 % of carriers are thought to harbour HTLV-1 in more than 5 % of peripheral blood CD4+ T cells [10] and it is within this subset of patients with high proviral load that ATLL is thought to emerge [11, 12]. Thus, malignant transformation of a HTLV-1 infected CD4 cell appears to be a relatively rare event following a long period of clinically latent infection. This suggests that viral infection alone is insufficient and further accumulation of genetic events is required to progress to the malignant phenotype.

The pathogenesis of ATLL is poorly understood. After a limited number of replication cycles using reverse transcriptase (infectious spread) during primary infection, HTLV-1 replicates and increases its proviral copy number through the proliferation of infected cells using cellular DNA polymerases (mitotic spread). The viral protein Tax is important in leukemogenesis and in vitro Tax alone is sufficient to transform lymphocytes. However, in ATLL Tax expression is frequently disrupted and often silenced. Clonal proliferation of CD4+ infected cells is likely to be linked to the pleiotropic effects of Tax, a viral transcription activator protein [13] which in vitro induces expression of several cytokines such as IL-2 and IL-15, resistance to induction of apoptosis, and promotion of genetic instability [14, 15]. More recently HTLV-1 basic leucine zipper protein (HBZ), encoded on the minus strand of the HTLV-1 provirus has been implicated in ATLL pathogenesis mainly through modulation of cell signalling pathways which are related to cellular proliferation, immune responses and T cell differentiation [16•].

The initial HTLV-1 mediated T cell transformation arises from several multistep oncogenic processes resulting in chronic T cell proliferation and deregulated growth of infected cells [17].The genetic abnormalities accumulating in these cells eventually generate a pre leukaemic phase followed by a leukaemic state. Because of this, an acquired state of T-cell deficiency develops resulting in susceptibility to a variety of opportunistic infections. In 1988 Moriyama et al., described cases of Pneumocystis jirovecci pneumonia in two HTLV-1 carriers from Japan with low CD4 counts [18]. Strongyloides sterocalis (SS) infection is persistent among seropositive carriers and recent studies have revealed an association between SS and acute or lymphomatous ATLL suggesting that infection by SS infection might play a role as a cofactor in HTLV-1 mediated transformation [19]. Recent studies into the underlying immune deficiency of HTLV-1 infection have revealed that HBZ suppresses transcription of the IFNγ gene promoter by inhibiting NFAT and AP-1 signalling pathways [20]. The clinical importance of this is however uncertain as the majority of HTLV-1 infection is in carriers who remain asymptomatic throughout this lifelong infection. However, there is a general acceptance that immune suppression in patients with ATLL is more profound than with other lymphoproliferative diseases and routine antimicrobial prophylaxis is important to prevent opportunistic infections, which have been a major contributor to ATLL-driven mortality.

Why Is the Prognosis of ATLL So Poor?

ATLL treatment results have been disappointing and remain a significant clinical challenge. Very few patients respond successfully to chemotherapy regimens [6]. Resistance to chemotherapy is multifactorial with mutations in P53, impaired regulation of oncogenes and Multi Drug Resistance gene (MDR) overexpression in ATLL cells as contributing factors [6, 21].

When patients present with aggressive ATLL, the prognosis is poor because of intrinsic chemo resistance, a large tumour burden, hypercalcaemia and frequent infectious complications due to the underlying intrinsic cellular immune deficiency. Because of the differences inherent in the geographical locations of the disease in Asia, the Americas and Europe, there is no worldwide consensus on the optimal treatment approach. Little is known about ATLL in Africa.

Chemotherapy Approaches

With chemotherapy alone survival is measured only in months and relatively few patients are able to progress to stem cell transplantation as a consolidation procedure although transplantation rates vary by region. Problems encountered include failure to achieve complete remission, early relapse, age of presentation and finding a suitable donor. The first clinical trials for ATLL were performed in Japan between 1978 and 1983. CHOP has been the mainstay of therapy and during the 1980's and 1990's resulted in median survival of 5–10 months (Table 1). Further CHOP-like regimens were tested, but despite relatively high overall response rates, this did not translate into enhanced survival rates suggesting that an increase in dose intensity may be required to increase overall survival rates.

Table 1 ATLL: Chemotherapy regimens

Year	Regimen	No	CR (%)	PR (%)	Response rate	Median survival rates	Survival rate	Author
1980's	CHOP / CHOP Like	Various	18 %	N/A	N/A	~5–6 Months	NA	Shimoyama 1988
1996	CHOP followed by Etoposide/vindesine/Ranimustine and mitoxantrone/GCSF	81	36 %	38 %	74 %	8.5 Months	3 Year	Taguchi,H et al. 1996
		44 Acute					OS	J Aids
		37 Lymphoma					13.5 %	
2001	LSG 15: VCAP/AMP/VECP/VACP VCAP(Vincristine,cyclophosphamide, doxorubicin, prednisolone), AMP (Doxorubicin,,ranimustine,prednisolone), VECP(Vindesine,etoposide,carboplatin, prednisolone)	96	35.5 %	45.2 %	81 %	13 Months	2 Years	Yamada et al. BJH 2001
		58 Acute 28Lymphoma					31.3 %	*Value of dose intensity confirmed
		10 UC						
2003	Deoxycoformycin (JCOG 9109)	62	28 %	24 %	52 %	7.4 Months	2 year Estimated 15.5 %	Tsukasaki K et al. 2003
		34 Acute						Int J Hematol
		21 Lymphoma 7 UC						*DCF abandoned
2007	VCAP-AMP-VECP	118	VAC 40 %	VAC 32 %	VAC 72 %	13 Months VAC	3 Year	Tsukasaki K
							OS	
	Compared to bi-weekly CHOP/GCSF (JCOG9801)		CHOP 24 %	CHOP 41 %	CHOP 65 %	11 Months CHOP	24 % VAC	JCO 2007
							13 % CHOP	*Dose intensity regimen superior to CHOP
2011	Phase II CHOP+D25 ab	15	33 %	20 %	53 %	10/12 in high responders	CR patients	Caesay,M et al. 2011
		11 Acute 4 Lymphoma					DFS 15/12	Leuk Res

In 2001 a new Japanese protocol using an alternating intensive chemotherapy regimen (LSG 15) produced a two year overall survival rate of 31.3 % with a median survival of 13 months [22].To date this has been the most successful first-line chemotherapy modality for ATLL. In a direct comparison, the LSG 15 protocol was superior to CHOP (CR 25 %) with complete remission rates of 40 % (p=0.02) [23]. Moreover the 3 year survival rate was 24 % for LSG15 compared with 13 % for CHOP defining this regimen as the standard of care for ATLL in Japan.

Further Modalities to Treat Aggressive ATLL – Targeted Therapies: Antiviral Therapies

Despite this improvement, outcomes with chemotherapy alone remain poor for the majority of patents. In order to circumvent chemotherapy resistance alternative, biological targets are needed. One approach which has been shown to improve the survival of patients with ATLL is the combination of the thymidine analogue, zidovudine (ZDV) with interferon alpha (IFN). The use of this 'antiviral' combination therapy is largely serendipitous. Zidovudine was demonstrated to prolong survival of patients with HIV and the acquired immune deficiency syndrome in 1987 whilst the anti-viral efficacy of interferon has been known since the 1980s [24].In the early days of HIV therapy, Shibata et al. [25•] treating a patient co-infected with HTLV-1 and HIV-1 reported sustained improvement in ATLL following ZDV/IFN treatment. The authors pursued this anecdotal finding with a case series, the results of which were published back-to-back with data from a French group in the New England Journal of Medicine in June 1995. Gill et al. [26•] reported major responses in 11/19 patients treated with combination therapy (five complete remissions and six partial responses). Seven of these 19 patients exhibited relapsed or refractory disease. Hermine et al., demonstrated rapid and durable responses in five patients with ATLL [27•]. A succession of open studies supported these early encouraging results reporting response rates of 65–92 % with more than 50 % achieving complete remission [28, 29] (Table 2). Despite these data, 'antiviral therapy' for ATLL has not been universally accepted and many questions remain: What is the optimal dose? When to administer? What is the duration of treatment? Is antiviral therapy alone sufficient? Can all subtypes be treated the same?

High doses of both drugs were used in these studies: Zidovudine 500 mg–1 g/day in divided doses and alpha interferon 6–9 million units subcutaneously daily. Is this optimal and how well tolerated are these doses, particularly if given with chemotherapy? : The significant differences in outcome between the more indolent chronic/smoldering and the aggressive acute/lymphoma subtypes need to be considered when evaluating treatment studies, between acute and lymphoma subtypes there are substantial differences in tumour bulk which may impact prognosis and inter-patient variation in presentation may dictate the need for a more rapid response. It is therefore interesting to note in these early papers that certain groups in the analysis appeared to achieve longer overall survival times (Table 2). In the absence of randomised controlled studies such questions can be difficult to address. However, the absence of consensus and site by site differences in approach has allowed two retrospective analyses to further tease out the beneficial effects of antiviral therapy according to subtype [30•, 31•] and timing of therapy [31•].

ATLL: Meta-Analysis Results 2010 [30•]

In this paper participating centres reported their outcomes with the use of antiviral therapy alone, antiviral therapy plus chemotherapy and chemotherapy alone. Data on 254 patients treated in the United States, the United Kingdom, Martinique and continental France were collated. According to the Shimoyama classification [8•] 116 patients had acute ATLL, 18 patients chronic ATLL, 11 patients smoldering ATLL, and 100 patients ATLL lymphoma.

First line therapy data was recorded in 207 patients. Five year overall survival was 46 % for all patients who received antiviral therapy alone (n=75) 14 % for those who never received antiviral therapy (n=132) and 12 % for those who received first line chemotherapy followed by antiviral therapy (n=55) (p=0.004). The immediate conclusion is of a survival advantage for patients who received antiviral therapy in their initial treatment but there are likely to be inherent biases with the potential for sicker patients to be treated immediately with chemotherapy. To elucidate which groups benefited most, a subtype analysis was undertaken. Patients with acute, chronic or smoldering ATLL significantly benefited from antiviral therapy whereas those with lymphoma ATLL experienced a better outcome with chemotherapy. The best results with antiviral therapy were seen in patients with chronic or smoldering ATLL (n=17) with 100 % 5 year overall survival rate in contrast to a 42 % 5 year to those treated with chemotherapy alone.

Within the acute leukaemic subtype there appeared a subgroup of patients who achieved CR with antiviral therapy alone and a 5 year survival rate of 82 %. This result echoes some of the phase II data where patients who entered CR achieved prolonged survival [29] suggesting that in these patients the biology of the tumour may be permissive to treatment with antiviral therapy alone. Subsequent multivariate analysis confirmed that first line antiviral therapy significantly improved overall survival of patients with ATLL (HR, 0.47; CI 0.27 to 0.83 ; p=0.021). Criticism which could be levelled with this analysis was that it was

Table 2 ATLL: Antiviral results

Country of origin	Therapy	No	ATLL subtype	Disease status	Response to AVT	Survival	Reference comments*
USA	IFN/ZDV	19	Acute 17 Lymphoma 2	De Novo 12 Refractory/ Relapsed 7	58 % CR+PR 11 Major/Partial 8 minor response	Median survival for CR/PR patients 13/12	Gill et al. 1995 NEJM
France	IFN/ZDV	5	Acute 4 Lymphoma 1	De Novo	2CR,3PR	Median Survival 10/12	Hermine et al. 1995 NEJM
UK	IFN/ZDV	15	Acute 11 Lymphoma 2 Smouldering 2	12 Relapsed 3 De Novo	67 % CR+PR	Median Survival 18/12	Matutes et al. 2001 BJH
USA	IFN/ZDV	18	Acute 11 Lymphoma 5 Chronic 5	15 Relapse/ Refractory 3 De Novo	1CR/2PR/5SD/4PD/6NE	Median 6/12	White et al. 2001 *Heavily pre treated
French West Indies	2XCHOP+IFN +/− ZDV or ddC +Etoposide	29	Acute 16 Chronic 3 Lymphoma 10	De Novo	NA	Median Survival 8/12	Besson et al. 2002 Leuk and Lymphoma
France	CHOP +/− IFN/ZDV	19	Acute 15 Lymphoma 4	13 De Novo 6 Relapse	53 % CR 25 % PR	Median Survival 11/12	Hermine et al. 2002 Haematol J *Note CR patients OS 28/12*
USA/ Caribbean	IFN/ZDV	38	Acute 21 Chronic 4 Lymphoma 13	21 De Novo	22.7 % CR 18.2 % PR	Median follow up 5/12	Ramos et al. 2007 Blood *No responders in Lymphoma Group
USA	EPOCH followed by IFN/ZDV/Lamivudine	19	Lymphoma N/A Acute N/A	De Novo	11 % CR 47 % PR	Median survival 6/12	Ratner et al. 2009
Worldwide	First Group 1st Line AVT IFN/ZDV Second Group Chemotherapy +/− AVT	254	Acute 116 Chronic 18 Smoldering 11 Lymphoma 100	De Novo	First Line AVT 35 % CR 31 % PR 34 % NR	First Line AVT(n=75) 5 Year OS 46 % First line chemotherapy (n=77) 5 Year OS 20 % Chemotherapy followed by AVT (N=55) 5Year OS 12 %	Bazarbachi et al. 2010 JCO *AVT for Chronic / Smoldering 100 % 5 Year OS Acute : CR with AVT 82 % 5 Year OS
UK	Chemotherapy +/− IFN/ZDV	73	Acute 29 Lymphoma 44	De Novo	Chemotherapy Alone: ORR 49 % Chemotherapy with AVT ORR 81 %	Median OS: 10/12 Lymphoma 7.5 /12 Acute	Hodson et al. 2011 JCO *Combined modality therapy increased median OS for Acute and Lymphoma types

retrospective and did not report efficacy of chemotherapy alone from the Japanese cohorts where the use of antiviral therapy has not been adopted. However at least in the predominantly Afro-Caribbean populations treated at the participating centres, the results were indicative of a clear overall benefit with antiviral therapy alone in the treatment of the leukaemic forms of ATLL. However, whilst antiviral therapy alone has become the preferred first-line treatment for patients with chronic ATLL with excellent outcomes, the situation for patients with acute leukaemic ATLL is less clear. A subgroup clearly responds well to antiviral therapy alone. How can they be identified and spared chemotherapy? More detailed phenotyping of IRF-4 [44•] and TP53 [42•] has been suggested and further studies to validate the predictive capacity of this are needed. If these are not available and until validated, the only effective approach is to initiate antiviral treatment in all patients with acute ATLL with the clear understanding and expectation that perhaps one third will respond well, achieve CR and can expect prolonged survival (without transplantation). The corollary is that there needs to be a clear understanding by clinician and patient alike that in 2/3 resort to traditional approaches will be needed.

ATLL: UK Data [31•]

A second retrospective study by Hodson et al. in 2011 [31•] reported treatment outcomes in 73 patients with aggressive ATLL who were diagnosed between 1999–2009. In particular, the impact of the use of antivirals was assessed. The aims of the study were to define the response rates in ATLL and by subtype, to look at the effects of antiviral therapy in subtype response rates and survival outcomes compared to chemotherapy alone. Overall response rate recorded for all patients treated with combined first line therapy (defined as chemotherapy with concurrent or sequential ZDV/IFN) was 81 % as compared to 49 % with chemotherapy alone. The benefit of the use of antiviral treatment at any time in the treatment journey was observed for both the acute and lymphomatous subtypes. The use of ZDV/IFN at any time prolonged survival in acute ($p<0.001$) and lymphoma ATLL ($p<0.001$) and was the sole factor associated with reduction in risk of death in aggressive ATLL (HR 0.23; 95 % CI 0.09 to 0.60; $p=0.002$). The combined use of antiviral therapy prolonged median OS in acute ($p=0.0081$) and lymphoma ATLL ($p=0.001$) compared to chemotherapy alone.

The results of the UK analysis confirmed the results of the met analysis in acute ATLL, and additionally showed that combined modality therapy was beneficial for the lymphomatous subtype. The results obtained for the lymphomatous subtype were similar to those obtained by the Japanese Clinical Oncology study group for LSG15 suggesting the extra dose intensity of the intensive Japanese regimen could be matched by the addition of antiviral therapy to CHOP-like chemotherapy. It should be noted that in the UK series the antivirals were used at much lower doses (recommended doses Interferon-α 3 million units daily and ZDV 250 mg bd) than in the met analysis patients where doses were typically AZT 500 mg to 1 g daily and Alpha interferon 6–9 mu daily. A prospective trial comparing the two options would be required to determine the more optimal approach. An interesting and unexpected finding of the UK study was that the timing of first exposure to antiviral therapy did not impact outcome. Some patients initiated antiviral therapy with chemotherapy, some immediately after completing a course of chemotherapy and some after an interval. Larger numbers of patients will be needed to tease out any differences in efficacy and toxicity but the key message was to offer antiviral therapy at some point. Neither study has addressed the optimal duration of antiviral therapy. Our current practise is to continue with antivirals for up to 5 years, if tolerated. The median duration of antiviral therapy in these long-term survivors is 12.6 months

Japanese Experience with Antivirals

In Japan, a major endemic area for HTLV-1 related disease, the use of antiviral therapies has not been extensively tested. A small Japanese series reported by Ishitsuka et al. [32] in 3 patients with refractory and relapsed ATLL who were treated with ZDV/IFN demonstrated some anti ATLL effect with stabilisation of disease rather than induction of remission. In Japan the standard of care for patients with indolent disease has been watchful waiting which reported a 5 year OS of 47 % [33],which contrasts sharply with the results obtained by Bazarbachi et al., with a 100 % 5 year survival rate reported [30•]. Therefore, in order to test out the promising potential of antivirals in indolent ATLL, the Japanese Lymphoma study group (JCOG) are carrying out a randomised phase III study which will compare the outcome of watchful waiting versus ZDV/IFN.

Mechanisms of Action of "Antivirals"

The success achieved with antivirals raises the question of how these agents act. Are the effects anti proliferative, antiviral or directly cytotoxic?

The Interferons

The interferons are a family of glycoproteins which have potent antiviral effects. They can activate several interferon

responsive genes that have direct antiviral activity by inhibiting viral replication, increasing expression of HLA class I molecules leading to increased recognition of CTL killing of infected lymphocytes [34].The interferons have multiple actions which include induction of 2′-5′oligoadenylate synthase and protein kinase P1, suppression of cellular proliferation, direct immunomodulation such as direct stimulation of immune effector cells populations such as natural killer cells and macrophages, increased antigen presentation to lymphocytes, induction of the resistance of host cells to viral infection, slowing of tumour cell growth and inhibition of viral replication in cells. A recent report suggests that HTLV-1 infected cells evade type 1 IFN signalling by inducing the suppressor of cytokine signalling SOCS1 expression [35]. It is also known that interferons may inhibit HTLV-1 virus assembly by preventing targeting of viral Gag proteins to the rafts in the plasma membrane [36]. Further immunological effects may be mediated by direct cytotoxic effects to HTLV-1 infected cells.

The direct antiviral effects of the combination have been shown in animal models with reduction in HTLV-1 proviral load [37], and in vitro with inhibition of transmission of HTLV-1 to adult peripheral blood mononuclear cells and prevention of transformation of these normal blood lymphocytes when co–cultured with an HTLV-1 transformed cell line [38]. Furthermore, the combination of ZDV with a histone deacetylase inhibitor (HDI) has been shown to decrease proviral load and increase virus specific CTL responses in a baboon model infected with the simian homologue STLV-1 [40]. As it is difficult to demonstrate direct viral replication in ATLL cells, the mechanism of how viral load is decreased is unknown but this does raise the question that falling viral loads observed may arise as a result of a direct effect of inhibition of viral replication in a reservoir outside the blood pool.

Zidovudine

ZDV is a pyrimidine nucleoside analogue that inhibits the reverse transcriptase of the human immunodeficiency virus (HIV) and HTLV-1 virus. Incorporation of the active metabolite, zidovudine triphosphate, terminates the extension of the DNA chain. ZDV also inhibits telomerase which results in progressive telomere shortening and direct induction of cellular senescence and activation of the pro apoptosis factor $P14^{ARF}$ and activation and stabilisation of TTP53 in cases of ATLL and HTLV-1 cell lines [41, 42•]. Importantly, the presence of wild type TTP53 is important for ZDV efficacy and a study revealed that in patients with acute or chronic ATLL wild type TP53 was present in 82 % of cases [43].

Resistance to Antiviral Therapies

The results from the early phase II studies indicated that a proportion of patients with aggressive ATLL treated with antiviral displayed increased overall survival rates if they entered a complete remission. Preliminary data indicate that in vitro, pre-treatment of ATLL cells with ZDV inhibits telomerase function accelerating cellular senescence rather than a direct cytotoxic effect. The same study also showed the ability to reactivate normal TTP53 gene functional status. In a study of 14 patients with ATLL, five had wild type TP53, two (one chronic/one smoldering) achieved CR with ZDV/IFN, two patients with acute ATLL achieved PR and one patient with chronic ATLL relapsed with switch from wild type to mutated TP53. Of the nine patients in whom TP53 was mutated at baseline, only one (PR) responded to ZDV/IFN [41].This suggests that TP53 genotyping or phenotyping might be useful to identify the patients who will respond to this therapy.

In an effort to further predict sensitivity to antiviral therapy, Ramos et al. [44•] studied primary ATLL tumours and identified molecular features linked to sensitivity and resistance to antiviral therapy. In this study of 28 patients, elevated expression of Interferon regulatory factor 4, a target of the c-rel subunit of NF-Kb, was observed in 91 % of nonresponders. In contrast, patients who were complete responders did not express c-Rel or IRF-4. Because the combination of IFN alpha and AZT is suppressive rather than curative, it was concluded patients who enter remission should remain on indefinite treatment.

In the study of Ramos et al., IRF-4 over expression was observed in nearly all of the patients with the lymphoma subtype and this was thought to be one of the reasons of the relative poor efficacy of antiviral therapies in this group of patients. In gene expression studies, Alizadeh reported that the combination of AZT and interferon induced upregulation of interferon responsive genes with silencing of cell cycles associated genes. Patients who failed to respond ZDV/IFN failed to show the interferon response signature in a comparison of tumour gene signatures pre and post treatment [45].

Other Antiviral Agents

Because of the mechanism of action of nucleoside agents with anti reverse transcriptase activity, other agents have also been tested such as tenofovir, lamivudine and zalcitabine and have demonstrated some activity. Lamivudine has also been shown to reduce proviral load in patients with HTLV-1-associated myelopathy [38]. It is worth noting the HTLV-1 RT susceptibility of primary viral isolates differed from the susceptibility of HTLV-1 from chronically infected cell lines [39].

Future Directives with Antiviral Therapy – Combination with Arsenic Trioxide

In order to develop effective therapies for ATLL, international collaborative studies are required to test prospectively novel agent therapies. Bazarbachi et al., demonstrated that arsenic trioxide synergises with IFN to induce cell cycle arrest and apoptosis in HTLV-1 infected cells through rapid shutdown of the NF-kappa B pathway. The authors subsequently used the combination of arsenic and interferon in seven patients with relapsed refractory ATLL. One patient entered complete remission and, in three, partial remission was obtained [46]. In a further study of 10 patients with chronic ATLL, a 100 % response rate was observed including seven with CR [47]. As biological basis for these results, the authors were able to demonstrate in a Tax transgenic marine model that arsenic and interferon can cure murine ATLL by selective eradication of leukaemia – initiating cell suggesting that LIC activity was dependant on continuous tax expression [48]. Given the antiviral efficacy of interferons and ZDV in combination, other novel therapies may be appropriate and there is evidence that ZDV in combination with HDI decreases proviral loads. It is worth noting that in this study neither compound alone reduced proviral load.

Conclusion

The benefit of antiviral therapy with ZDV/IFN in the treatment of ATLL has now been repeatedly demonstrated over a period of 15 years. The benefit appears to be most in the leukaemic types particularly chronic ATLL in which ZDV/IFN alone should now be the first line of therapy whilst recent evidence has suggested benefit too in the lymphomatous subtype when used in conjunction with chemotherapy. The appropriate use of these agents will be enhanced by risk stratification of patients determined by more easily available diagnostic investigations which predict response to treatment such as gene sequencing to detect TP53 mutation(s) and IRF-4 expression. In order to confirm the results of the previous retrospective studies, randomised prospective studies are required which will yield definitive answers. Unanswered questions still remain as to optimal dose of antiviral therapy and in particular whether the high doses of antiviral agents is equivalent to lower doses plus additional chemotherapy. The observed overall response rates achieved with these strategies may improve the number of patients that access potentially curative consolidation strategies such stem cell transplantation, but this approach should be considered in the light of the long term survival of the subgroup that achieve CR and survive beyond 24 months in whom the survival curve appears to level out. Despite these benefits of ZDV/IFN, which have already impacted on the median survival of chronic and aggressive ATLL, for the majority of patients the prognosis remains poor. Therefore there is a continuing need for novel biological targets which may be used alone or in combination with antiviral agents. The limited data around the combination of IFN/Arsenic and ZDV in combination in induction and IFN/Arsenic as a consolidation therapy requires confirmation. There is already some experience with monoclonal antibodies in the treatment of ATLL with several studies of anti-CD25, whilst an anti CCR4 antibody currently in clinical trial T cell NHL and for relapsed or refractory ATLL looks promising [49•].

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