## Pathogenesis

### *Hypercalcemia*

Hypercalcemia complicates more than 70% of ATL cases during the entire clinical course (Kiyokawa *et al.*, 1987), and the extent of hypercalcemia is frequently severe. In the bone of hypercalcemic patients, the number of activated osteoclasts increases, which accelerates bone resorption. In the differentiation of osteoclast from the hematopoietic precursor cells, RANK ligand, which is expressed on the osteoblasts, and M-CSF cooperatively induce the differentiation of osteoclasts (Arai *et al.*, 1999). In hypercalcemic ATL patients, ATL cells have been shown to express RANK ligand (Nosaka *et al.*, 2002), and the serum level of M-CSF is elevated in most ATL patients. ATL cells from hypercalcemic patients have been demonstrated to induce the differentiation of hematopoietic precursor cells into osteoclasts *in vitro*. These data indicate that ATL cells expressing RANK ligand induce the differentiation to osteoclast, and such increased osteoclasts accelerate bone resorption, resulting in hypercalcemia. In ATL patients, parathyroid hormone-related peptide (PTH-rP) is frequently increased (Watanabe *et al.*, 1990), which induces the RANK ligand expression on osteoblasts. Increased PTH-rP is also implicated in ATL-associated hypercalcemia.

### *Immunodeficiency*

Opportunistic infections are frequent complications in ATL patients, and impaired cell-mediated immunity has been identified as a causative basis of immunodeficiency. Pathogens of opportunistic infections include *Pneumocystis jiroveci*, cytomegalovirus, *Strongyloides stercoralis*, and a variety of fungi. Such infections are one reason for the poor prognosis, despite treatment, of ATL patients. Mild immunodeficiency is also seen in asymptomatic carriers (Katsuki *et al.*, 1987; Welles *et al.*, 1994). Here, a decreased number of naïve T-lymphocytes is proposed as a cause of immunodeficiency (Yasunaga *et al.*, 2001). CD4+, CD25+ T cells are reported to have immunoregulatory functions, and are called as regulatory T cells (Treg). Tregs have suppressive immune functions. Tregs express *forkhead box P3* (*FOXP3*) gene, which is a master gene of immunoregulatory functions (Fontenot and Rudensky, 2005). ATL cells show the phenotype of activated helper T cell (CD4+ and CD25+), suggesting that they are derived from a Treg cell. *FOXP3* gene transcription was detected in eight of 17 ATL cases (47%) (Karube *et al.*, 2004). Such Treg phenotype of ATL cells is considered to suppress the immune response, and may be implicated in the immunodeficiency. In addition to the FOXP3+ Tregs, antigen-induced IL-10 secreting Tr1 has been identified as another subset of Treg (Thompson and Powrie, 2004), which is FOXP3 negative. Although FOXP3 expression was not detected in about half of ATL cases, ATL cells were reported to produce IL-10 suggesting that FOXP3-negative ATL cells also have regulatory contribution.

## Treatment of ATLL

After 28 years of the initial description of ATLL as a discrete clinical entity, this condition continues to carry a very poor prognosis. Recent reviews cite median survivals of less than 1 year despite advances in both chemotherapy and supportive care (Siegel *et al.*, 2001). The 6 months median survival of Japanese patients with ATLL reported in Shimoyama's (1992) overview does not significantly differ from experience in Europe a decade later (Taylor *et al.*, 2001). It is therefore hard to disagree with Yamada and Tomonaga's conclusion that the vast accumulation of knowledge in the molecular biology and oncogenesis of ATLL has yet to be translated into an improved prognosis (Yamada and Tomonaga, 2003). Yet, the array of therapeutic approaches tested over the past two decades is impressive. In this section, we review extant data and attempt to determine why so many therapies, initially reported optimistically, have not been further developed. We look to how prognosis might be improved in the future.

### *Chemotherapy*

Cyclophosphamide, adriamycin, vincristine, and prednisolone (CHOP) has been, and probably remains, the standard first-line therapy for ATLL and many patients do exhibit either partial (PR) or complete remission (CR). Yet a literature search will reveal only limited data on the efficacy of this approach. Tsukasaki *et al.* reviewed the outcome of their cohort of 114 patients presenting with acute or lymphomatous ATLL between 1975 and 1989. These patients were treated with combination chemotherapy with only 17.5% achieving CR, but a further 46.5% had a partial response (Tsukasaki *et al.*, 1993). These data accord with the results of the Lymphoma Study Group in which CR was obtained in 17–18% of patients treated with CHOP (LSG-1) (Lymphoma Study Group, 1982; Shimoyama *et al.*, 1988); in 37% of patients treated with CHOP plus methotrexate (Shimoyama *et al.*, 1988). A similar response (63% CR+PR) was found in 21 patients treated with combination chemotherapy in London, UK over a 15-year period (1981–1995), but the median survival was only 5.5 months (Pawson *et al.*, 1998). Intensification of CHOP with etoposide, vindesine, ranimustine, and mitoxantrone resulted in CR in 35.8% of the 83 patients (Taguchi *et al.*, 1996) and in 43% when part of a nine-agent cycle (LSG-4) (Tobinai *et al.*, 1994). However, the median survival was only 8–8.5 months in these studies with predicted survivals of 13.5% after 3 years and 12% after 4 years, respectively. Matsushita *et al.* reported their experience of substituting etoposide for adriamycin in a weekly long-term maintenance chemotherapy. The median survival in their 79 patients with acute, lymphoma, and progressive

chronic ATLL following this regimen was 7.5 months, but the therapy was reported to be well tolerated (Matsushita *et al.*, 1999). Better survival, 18 months, was observed among a further eight patients treated with daily etoposide plus prednisolone, but this may have been due to selection bias. The best outcome with chemotherapy reported to date has been with an aggressive multidrug approach supported by G-CSF. While this regimen of seven cycles of VCAP (vincristine, cyclophosphamide, doxorubicin, and prednisone), AMP (doxorubicin, ranimustine, and prednisone), and VECP (vindesine, etoposide, carboplatin, and prednisone) was, as anticipated, highly marrow toxic with grade 4 haematological toxicity in the majority of patients, the median survival of 13 months among 96 treatment naïve patients with acute, lymphoma and progressive chronic ATLL does represent an improvement (Yamada *et al.*, 2001). The relative insensitivity of ATLL to chemotherapy may be related, at least in part, to upregulation of MDR gene (Kuwazuru *et al.*, 1990). In the Yamada study, ranimustine and carboplatin were included in the regimen because they are not affected by P-glycoprotein expression.

Part of the problem lies in the variable natural history of ATLL, and therefore the balance of disease types in the cohort may affect the outcome. For this reason, case reports are almost uninterpretable. In Uozumi's study, the median survival of 43 patients with acute and lymphoma ATLL treated with a response-orientated cyclic multidrug protocol was only 6 months, but many patients had poor prognostic factors (Uozumi *et al.*, 1995). While in Matsushita's cohort of maintenance therapy, the survival of patients with acute leukemia was 6.7 months, lymphoma 9.6, and progressive chronic leukemia 12.4 months (Matsushita *et al.*, 1999). It is difficult to judge whether this approach represents an advance in therapy as suggested by the authors although this remains a possibility. The best response rates are with the LSG-15 regime on which patients with acute ATLL survived 10.9 months and patients presenting with lymphoma 19.8 months (Yamada *et al.*, 2001). However, because renal dysfunction was an exclusion criterion, no patients with severe hypercalcemia were included in the study. This may have contributed to the superior results seen with this protocol. Overall, ATLL survival with various chemotherapy regimens is poor, with survival in several cohorts of patients presenting predominantly with acute leukemia or lymphoma ranging between 5.5 and 13 months. This approach does not offer the prospect of cure (Table 1).

### *Nucleoside analogues*

A number of studies have addressed the role of nucleoside analogues in the management of ATLL. The purine analog 2′ deoxycoformycin (DCF) that inhibits adenosine deaminase has been investigated as an alternative approach. In a phase I dose finding safety study, 3/18 patients with ATLL had a PR with 3 days intravenous (i.v.) therapy. The suggested dose for phase II trials was 5 mg/m$^2$ i.v. for 3 days (Tobinai *et al.*, 1992). In another study using DCF 4 mg/m$^2$/week for 4 weeks followed by fortnightly therapy, two CR and one PR were reported among 25 patients with ATLL (Mercieca *et al.*, 1994). While reported with a degree of optimism, these response rates are clearly lower than with CHOP-based chemotherapy. Using DCF in conjunction with chemotherapy, 52% of 60 patients achieved CR, but the median survival of all patients was only 7.4 months (Tsukasaki *et al.*, 2003).

Although one patient with treatment resistant acute ATLL had a prolonged partial response to another adenosine analog 2′ chlorodeoxyadenosine (cladribine) (Uike *et al.*, 1998), the follow-up phase II study showed very limited benefit in 15 patients, with only the one, presumably same, response reported. However, all patients had been treated with other agents prior to entering this study and therefore represent a poor prognosis group (Tobinai *et al.*, 2003). Another purine (adenosine) derivative has been studied in phase I. Dose-limiting marrow toxicity was observed with fludarabine phosphate (Arima *et al.*, 1999).

A parallel approach, using L-alanosine, an inhibitor of adenosine monophosphate synthesis, has been suggested based on the observation of increased sensitivity of ATLL cells to L-alanosine *in vitro*. A proportion of ATLL primary cells are deficient in methylthioadenosine phosphorylase (MTAP) which should make then more sensitive to purine synthesis inhibitors. Nonleukaemic cells can, *in vitro*, be protected from this effect by simultaneous treatment with 5′-deoxyadenosine (Harasawa *et al.*, 2002). No *in vivo* data have been published to date and the therapy would need to be selectively used in MTAP-deficient ATLL only.

### *Topoisomerase inhibitors*

Complete remission lasting 5 months after treatment with CPT-11, irinotecan hydrochloride, an inhibitor of topoisomerase I was reported in a patient with ATLL lymphoma unresponsive to intensified chemotherapy (Makino *et al.*, 1994). However in a study of 13 patients, all pretreated and failing chemotherapy, only one patient had a CR (Tsuda *et al.*, 1994). Although PR was seen in a further four patients, this agent has not been further studied in this group, in therapy naïve, nor in combination with other agents.

MST-16, a bis(2,6-dioxopiperazine) analog and inhibitor of topoisomerase II has been studied in a phase I–II trial (Ohno *et al.*, 1993). A total of 24 patients received 1200–2800 mg/day oral MST-16 for 7 days every 2–3 weeks. Remission occurred in both patients with chronic ATLL, 46% of patients with acute ATLL, but in only 25% of patients with lymphoma, and the two CR and eight PR lasted just over 2 months. These results do not represent an improvement over conventional chemotherapy and further studies with MST-16 have not been published.

Menogaril 100 mg daily 7 consecutive days every 3–4 weeks induced CR in 2/15 patients and PR in four (Taguchi *et al.*, 1997).

**Table 1** Therapy studies inclusive of acute, lymphoma, and progressing or poor prognosis chronic ATLL

| *First author* | *Year* | *Therapy* | *Support* | *N* | *CR (%)* | *PR (%)* | *ALL (%)* | *Median survival (months)* | *Survival rate* |
|---|---|---|---|---|---|---|---|---|---|
| Lymphoma Study Group | 1982 | CHOP (VEPA) aka LSG-1 | | | 18 | | | 6.0 | |
| Shimoyama, M | 1988 | VEPA v | | 54 | 17 | | | 6.0 | 4 years 8% |
| | | VEPA-M (aka LSG-2) | | | 37 | | | | |
| Tobinai | 1994 | VEPA-B/M-FEPA/VEPP-B (aka LSG-4) | | | 43 | | | 8.0 | 4 years 12% |
| Tsukasaki, K | 1993 | Combination chemotherapy (single institution cohort) | | 114 | 17.5 | 46.5 | 64 | | |
| Uozumi, K | 1995 | Response-orientated chemotherapy ?All treatment naïve | | 43 | 20.9 | 65.1 | 86 | 6.0 | |
| Taguchi, H | 1996 | CHOP + etoposide, vindesine, ranimustine and mitoxantrone | G-CSF | 83 | 35.5 | 38.3 | 74.1 | 8.5 | 3 years 13.5% |
| Pawson, R | 1998 | Combination chemotherapy | | 21 | | | 63 | 5.5 | |
| Matsushita, K | 1999 | OPEC/MPEC or etoposide/Pred (maintenance) | | 79 | 31 | 58.6 | 89.6 | 7.5 | |
| Yamada, Y | 2001 | VCAP/AMP/VECP (JCOG9309/ LSG-15) all treatment naïve | G-CSF | 96 | 35.5 | 45.2 | 81 | 13.0 | 2 years 31% |
| Tsuda, H | 1994 | CPT-II, topoisomerase-I inhibitor (refractory disease) | | 13 | 7.7 | 30.1 | 38.8 | | |
| Ohno, R | 1993 | MST-16, topoisomerase-II inhibitor | | 24 | 8.33 | 25.0 | 33.3 | | |
| Tsukasaki, K | 2003 | VPA/etoposide + deoxycoformycin aka LSG-11/JCOG9109 | | 60 | 28 | 24 | 52 | 7.4 | 2 years 17% |
| Gill, P | 1995 | Interferon-α + zidovudine (half had refractory/relapsed disease) | | 19 | 26.3 | 31.5 | 57.8 | 3.0 | |
| Hermine, O | 1995 | Interferon-α + zidovudine | | 18 | | | 66 | 10.0 | |
| Matutes, E | 2001 | CHOP, interferon-α + zidovudine | | 15 | | | 67 | 18.0 | |
| Hermine, O | 2002 | +/−CHOP, interferon-α + zidovudine | | 19 | 47 | 21 | 68 | 11.0 | |
| Besson, C | 2002 | CHOP, interferon-α + zidovudine, etoposide | | 7 | | | | 17.0 | |
| Waldmann, T | 1988 | Anti-Tac antibody | | 19 | 11 | 21 | 33 | | |
| Waldmann, T | 1995 | 90Y-labelled anti-Tac antibody | | 18 | 11 | 39 | 50 | | |
| Fukushima, T | 2005 | Allo-SCT | | 40 | 100 | | | 9.6 | 3 years 45.3% |
| *Acute ATLL only* | | | | | | | | | |
| Ohno, R | 1993 | MST-16, topoisomerase-II inhibitor | | 13 | 6.23 | 38.4 | 46.1 | | |
| Matsushita, K | 1999 | OPEC/MPEC or etoposide/Pred (maintenance) | | 51 | | | | 6.7 | |
| Yamada, Y | 2001 | VCAP/AMP/VECP | G-CSF | 56 | 19.6 | 53.6 | 73.2 | 10.9 | |
| Hermine, O | 2002 | +/−CHOP, interferon-α + zidovudine | | 15 | | | | | |
| *Lymphoma only* | | | | | | | | | |
| Ohno, R | 1993 | MST-16, topoisomerase-II inhibitor | | 8 | 0 | 25.0 | 25.0 | | |
| Matsushita, K | 1999 | OPEC/MPEC or etoposide/Pred (maintenance) | | 22 | | | | 9.6 | |
| Yamada, Y | 2001 | VCAP/AMP/VECP | G-CSF | 27 | 66.7 | 29.6 | 96.3 | 19.7 | |

Definitions of disease response (Yamada *et al.*, 2001): Complete remission – disappearance of all clinical and radiological evidence of disease and normalization of LDH for at least 4 weeks. Partial remission – greater than 50% reduction in disease for more than 4 weeks, and > 75% reduction in absolute abnormal lymphocyte counts, and LDH < 1.5 × normal upper limit

All-*trans*-retinoic acid (ATRA), an analog of vitamin A induces G1 cell-cycle arrest and induction of apoptosis in *ex vivo* ATLL cells. Exposure of cell lines derived from ATLL patient PBLs to ATRA results in increased cyclin D1 protein and an increase in complex formation with cyclin-dependent kinases 4 and 6 (cdk4/cdk6) and with proliferating cell nuclear antigen (PCNA). The effects of ATRA on these cell lines are complicated with evidence of an initial increase in cdk2 activity followed by depression of activity. Thus following ATRA, these cells were initially stimulated and then arrested in G1 (Dierov *et al.*, 1999).

### *Interferon*

Although ineffective alone, interferon-α does have a role in the management of ATLL especially in combination with zidovudine. The first report of potential benefit was the study by Ezaki *et al.* (1991) in which 9/12 patients, some pretreated with chemotherapy, had a PR with

human lymphoblastoid interferon in combination with bestrabucil (a combination of chlorambucil with β-estradiol). However, the treatment of all patients with lymphoma or hypercalcemia with prednisolone makes this result more difficult to evaluate.

*Zidovudine and Interferon plus zidovudine*

The observation of clinical improvement in ATLL in a patient undergoing treatment for HIV-1 infection with zidovudine plus interferon-α led to the further investigation of this combination. In the USA, Gill *et al.* treated 19 patients, seven relapsing after chemotherapy, with zidovudine 200 mg × 5/day plus interferon-α 5–10 MU s.c. daily, effecting CR in five and PR in six. Although four patients survived beyond 1 year, the median survival of only 3 months was indicative of the advanced disease in this cohort (Gill *et al.*, 1995). In France, Hermine *et al.* (1995) treated 18 patients with ZDV/IFN and achieved a 58% CR/PR response rate and a median survival of 10 months. In the UK, a debulking approach with 1–2 cycles of CHOP followed by a switch to lower doses of interferon-α (3–5 MU) plus zidovudine 500 mg bd was preferred. In total, 15 predominantly naïve, patients were treated in an open study, 67% achieving remission (CR + PR) with a median survival of 18 months (Matutes *et al.*, 2001). In a further phase II study from France of 12 treatment naïve patients with acute and lymphoma ATLL, the 92% response rate (seven CR and four PR) with zidovudine plus interferon-α represents a significant improvement over conventional and other chemotherapies (Hermine *et al.*, 2002). If all 19 patients, including the seven who did not receive ZDV/IFN first line, are included, the overall median survival remains a disappointing 11 months but 15/19 presented with the most aggressive, acute form of ATLL. Response and survival in patients who were treated with ZDV/IFN after initial chemotherapy was less impressive than those treated with ZDV/IFN as first-line therapy, but survival from initial presentation should also be considered. The Martinique experience, which is more similar to that of the UK, is to give two cycles of CHOP followed by ZDV/IFN (or sometimes the cytosine analog ddC instead of the thymidine analog ZDV) plus etoposide. The 17-month survival with this approach was significantly better than the historical survival of 3 months (Besson *et al.*, 2002).

*Interferon-α and arsenic trioxide ($As_2O_3$)*

*In vitro* studies have shown a synergistic effect of IFN-α and arsenic to induce apoptosis in ATLL cells. This combination was therefore offered to seven patients with refractory/relapsing ATLL in a pilot study. Although CR was seen in one patient persisting for a minimum of 56 months and PR in three patients, all patients had discontinued therapy after a median of 22 days due to toxicity or progression, and the six PR or unresponsive patients had died within a median of 1.5 months (Hermine *et al.*, 2004; Mahieux and Hermine, 2005). The median survival of these patients from first presentation (6 months prior to $As_2O_3$) was, therefore, 7.5 months. Arsenic alone has been shown to block transcription of NF-κB-dependent genes in HTLV-I-infected cells and in combination with IFN-α inhibits Tax-induced NF-κB activation (Nasr *et al.*, 2003).

*NF-κB blockade*

A number of apparently differing approaches point to the potential importance of NF-κB activity in ATLL and the therapeutic potential of NF-κB inhibition.

*In vitro* Bay 11-7082 inhibits NF-κB, reduces DNA binding to NF-κB, and downregulates transcription of Bcl-$x_L$. Preferential apoptosis of HTLV-I-infected cell lines and primary ATLL cells was observed. Unlike the histone deacetylation inhibitor, HFR901228, described below, Bay 11-7082 did not affect AP-1 (Mori *et al.*, 2002).

Inhibition of the proteasome by PS-341, bortezomib, blocking the degradation of IκBα and thereby inhibiting NF-κB has been shown to induce programmed death of ATLL cells *in vitro* (Tan and Waldmann, 2002; Satou *et al.*, 2004). Suppression of tumour growth was also documented in a SCID mouse ATLL model (Satou *et al.*, 2004). On the other hand, Tan and Waldmann (2002) reported no benefit in their mouse model of ATLL with PS-341 alone, but CR in some animals when combined with anti-Tac antibody.

The use of histone deacetylation inhibitors (HDIs) has recently attracted attention. One such compound, HFR901228, depsipeptide, has been shown to induce apoptosis in Tax-expressing and in Tax nonexpressing HTLV-I-infected cell lines and in primary cells for patients with acute ATLL. Its effect was through a reduction of DNA binding of NF-κB and AP-1, and downregulation of Bcl-$x_L$ and cyclin D2 expression. Partial inhibition of the growth of tumors, which result from the transplant of HTLV-I-infected cells, was seen in a SCID mouse model (Mori *et al.*, 2004). Sodium valproate, widely prescribed for the treatment of epilepsy, bipolar mood disorders, and migraine, has, among several potential antitumour properties, HDI activity (Blaheta and Cinatl, 2002). Sodium valproate is being studied as a maintenance therapy after chemotherapy for malignant glioma at a dose of 10–100 mg/kg/day. More importantly, dramatic clearance of both lymphoma and leukemia has been demonstrated in BLV-induced B-cell malignancy in sheep (Amine Achachi, Arnaud Florins, Nicolas Gillet, Christophe Debacq, Patrice Urbain, Germain Manfouo Foutsop, Fabian Vandermeers, Agnieszka Jasik, Michal Reicher, Pierre Kerkhofs, Laurence Lagneaux, Arsene Burny, Richard Kettmann, and Luc Willems: submitted for publication). While a trial of this therapy as part of the management of patients with acute and lymphoma ATLL should be considered further, possibilities include prevention of progression of chronic and smouldering ATLL. Should a protective effect be shown, the long-standing safety profile of this compound would justify a study to prevent ATLL in patients at higher risk of disease. The profile of such patients, high anti-HTLV-I

antibody titer and high soluble IL-2 receptor levels, has been described (Arisawa *et al.*, 2002).

*Monoclonal antibodies*

An alternative approach to the therapy of ATLL is to target cell differentiation markers on the malignant cells with monoclonal antibodies. The high expression of the IL-2$\alpha$ receptor, CD25, on ATLL cells has made this an attractive target. Waldmann first treated nine patients with ATLL with an anti-CD25 (anti-Tac) monoclonal antibody in the late 1980s. Responses lasting up to 8 months, including one CR, was seen in three patients (Waldmann *et al.*, 1988). Further evaluation of this agent in 19 patients revealed two CR and four PR (Waldmann *et al.*, 1993). Yttrium$^{90}$ labelling of the anti-Tac resulted in a small improvement in response with two CR and seven PR in 18 patients thus treated (Waldmann *et al.*, 1995). Eight patients were treatment naïve prior to the study and five had chronic ATLL. A humanized version of anti-CD25 was used in the next study with PR in 3/11 patients (Morris *et al.*, 2001). A study of humanized anti-CD25 antibody therapy supplementing standard CHOP chemotherapy is currently recruiting patients in the UK.

Another target is CD52. A humanized monoclonal anti-CD52 antibody, Campath-1H, effectively treated SCID mice infected with a tumor-causing HTLV-I-infected cell line. Treated mice surviving as long as HTLV-I unexposed mice (Zhang *et al.*, 2003). A National Institutes of Health (USA) sponsored phase II study of the safety and efficacy of Campath-1H in humans with ATLL (Protocol 03-C-0194) is recruiting (accessed 04/04/2005) http://clinicalstudies.info.nih.gov/detail/A_2003-C-0194.html. Unpublished data from five patients with relapsing ATLL treated at Kumamoto University Hospital indicate that while Campath-1H decreases ATL cells in the peripheral blood, it was not effective against lymphoma. The phenomenon of tumor enlargement during therapy with Campath-1H, previously observed in patients with NHL was also seen (Masao Matsuoka, unpublished).

*Transplantation*

The first published 'cure' of ATLL following bone marrow transplantation was in 1996. Following a 4-day infusion of cyclophosphomide, etoposide, and doxorubicin, the patient was grafted with cells donated from an HTLV-I-uninfected sister. After 2 years, HTLV-I could not be detected in peripheral blood by nested DNA PCR (Borg *et al.*, 1996) and the patient remains alive, disease free in 2005 (E Tholouli and J Yin, personal communication). Other case reports of allogeneic bone marrow transplantation with CR lasting at least 2 years with or without detectable HTLV-I genome followed (Tajima *et al.*, 2000; Ogata *et al.*, 2002). Molecular remission following autologous stem cell transplantation was reported, but the patient died of an opportunistic infection after 4 months (Nakane *et al.*, 1999). In a case series of 10 patients transplanted with allogeneic hematopoietic stem cells (Allo-SCT) (9/10 from HLA-identical siblings) after receiving total body irradiation and other conditioning agents, the median leukemia-free survival was >17.5 months but four patients died and in two ATLL relapsed (Utsunomiya *et al.*, 2001). In another series of Allo-SCT, one patient died within 30 days of transplantation but CR was seen in the remaining 10. However, six died of transplantation complications and the overall 1 year survival was only 53% (Kami *et al.*, 2003). The overall median survival from first presentation was >17.3 months and from Allo-SCT >12 months with four patients alive at the time of data census. A recent review of the outcome of 40 patients with acute or lymphoma ATLL, at seven centers in Japan, reported CR in all evaluable cases after Allo-SCT but a median survival time for all patients of only 9.6 months. The estimated 3-year overall survival of 45.3% compares favorably with historical data on chemotherapy. However, comparison across studies is always dangerous given the differences in support over time and potential selection bias (Fukushima *et al.*, 2005). The observation that some ATLL relapses could be successfully managed with a reduction in immune suppression supports the role of the graft versus leukemia effect (Harashima *et al.*, 2004; Okamura *et al.*, 2005).

PUVA can be useful for the management of cutaneous ATLL avoiding the toxicity of chemotherapy and other treatment modalities.

## Prevention of ATLL

The routes of transmission of HTLV-I are well documented. ATLL seems to be associated with transmission in early life. Possible factors for this association are the prolonged incubation period between infection and disease and primary infection before maturation of the immune system. Avoidance of breast-feeding by mothers known to carry HTLV-I reduces transmission by 80%. Whether limited breast-feeding for up to 3 months should be allowed, as some data suggest, is a difficult judgment but likely to be influenced by social and cultural factors. Prevention of mother-to-child transmission through breast-feeding should reduce the incidence of ATLL, although this will not be seen for many decades. Whether, HTLV-I infection acquired *in utero* or during delivery carries the same risk of ATLL (as breast milk associated transmission) is unknown. There have been no studies of either antiretroviral therapy or mode of delivery to address the potential for further reducing mother-to-child transmission. Screening for HTLV-I in pregnancy has been introduced in some endemic areas, including Japan and Martinique, but is much less widespread than screening of blood donors. The development of ATLL following blood transfusion acquisition of HTLV-I has rarely been reported.

Alternative approaches to the prevention of ATLL might include reducing HTLV-I proviral load by

antiretroviral therapy, targeted chemotherapy or immunotherapy, whether passive (monoclonal antibodies) or active. One suggestion has been the vaccination of HTLV-I carriers with high proviral load and low HTLV-specific T-cell responses with a HTLV-I Tax-targeted vaccine (Kannagi *et al.*, 2004). ATLL-like lymphoproliferative disease in rats has been prevented by adoptive transfer of T cells immunized with HTLV-I Tax DNA (Ohashi *et al.*, 2000). This is analogous to the control of post-transplantation EBV-associated lymphoproliferation by reducing immune suppression or by infusion of EBV-specific CTL. However, the association between immune suppression and ATLL is complex. A strong and persistent response to HTLV-I infection is found in patients with inflammatory disease and asymptomatic carriers and to date no association between a lack of response and subsequent development of ATLL has been shown. The proliferation of the malignant cell, diluting, or replacing circulating virus-specific T cells may contribute to any apparent lack of cellular response to HTLV in patients with ATLL. HTLV-I-specific responses can be found in PBL from patients with ATLL (Arnulf *et al.*, 2004).

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