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REVIEW

# Hematopoietic SCT for adult T-cell leukemia/lymphoma: a review

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**Adult T-cell leukemia/lymphoma is a T-cell malignancy caused by the human T-cell lymphotropic virus type 1. The aggressive forms of the disease carry a poor prognosis with standard therapies. The role of high-dose treatment with blood and marrow transplantation has, therefore, been examined mainly by Japanese groups in the form of retrospective studies. In this study, we review the literature, discuss some of the challenges facing successful transplantation approaches and stress the need for more innovative studies including in the Western hemisphere.**
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## Introduction

Adult T-cell leukemia/lymphoma (ATLL) is a post-thymic (peripheral) T-cell malignancy caused by the human T-cell lymphotropic virus type 1 (HTLV-1). The initial cases of ATLL were described in 1976 by Takatsuki, who reported on a series of 16 patients. All patients were born in the same region of Japan, thus suggesting that a transmissible agent may have been involved in the disease pathogenesis.[1–3]

The distribution of patients with ATLL is strongly linked to the endemic areas of HTLV-1. That is, southern Japan, the Caribbean, Melanesia, sub-Saharan Africa, and Central and South America which have the highest prevalence of ATLL.[4,5] ATLL occurs predominately in adults, typically between the ages of 20 and 80 years with a median age at the time of diagnosis in the 60s. It is more common in males (male:female ratio is 1.5:1).[6] There are roughly 15–20 million people infected with HTLV-1 worldwide, and the common modalities of transmission are sexually, vertically (mother–child), breast feeding or parenteral (for example, injection drug use and blood transfusion).[3,7–9] In the United States and Europe, the seroprevalence of HTLV-1 is $<1\%$, but increases up to 20% in injection drug users.[2,10] The lifetime risk of developing ATLL in individuals infected with HTLV-1 before the age of 20 is 5%.[3,6,9] There seems to be a genetic susceptibility to developing ATLL. HLA alleles A26, B4002, B4006 and B4801 predispose to the development of ATLL.[11,12]

The most recent WHO Classification of Tumors of Hematopoietic and Lymphoid Tissues[6] recognizes four distinct variants of ATLL, namely, acute (60%), lymphomatous (20%), chronic (15%) or smoldering (5%).[13] More recently, a smoldering primary cutaneous variant has also been described the acute ATLL variant usually presents with a leukemic phase with an elevated white blood count, skin lesions (erythematous rash, nodules or papules), generalized lymphadenopathy and hepatosplenomegaly. Hypercalcemia is common and is seen in 70% of patients. An elevated lactate dehydrogenase and eosinophilia are commonly seen as well.[14] The lymphomatous-type variant usually presents with marked lymphadenopathy but with no peripheral blood involvement. As with the acute variant, most patients present with aggressive advanced disease. Skin involvement is usually present, but hypercalcemia is less common.[4,15] The chronic variant typically presents with an exfoliative skin rash and less prominent peripheral blood findings. Finally, the smoldering variant usually has a normal WBC with $<5\%$ circulating neoplastic cells and there is no associated hypercalcemia. Similar to the chronic variant, the smoldering type has a 25% risk of transforming to the acute phase.[4] The acute and lymphomatous variants have the worst prognoses with a median survival of 6 months and 10 months, respectively. This is because of the aggressive clinical features, such as rapid cellular proliferation rate, large tumor burden with frequent multiorgan failure, hypercalcemia and frequent infectious complications.[15] The mean survival time for the smoldering variant is the longest of the four subtypes at over 2 years, whereas the chronic variant has a mean survival time of $\sim 2$ years. Death is most often caused by infectious complications, uncontrolled hypercalcemia or progressive disease.[3,15]

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## Non-transplantation therapeutic options

*Chemotherapeutic options*

Several combination chemotherapy regimens have been evaluated in patients with ATLL. The results have been disappointing with a median survival ranging between 7 and 13 months at best. More recently, a multicenter Japanese phase III trial randomized 118 patients with untreated aggressive ATLL to a combination of VCR, CY, doxorubicin, prednisone, ranimustine, vindesine, etoposide and carboplatin known as VCAP-AMP-VECP or biweekly CHOP.[16] Patients in both the arms received intrathecal chemotherapy and G-CSF support. The complete response rate was higher in the VCAP-AMP-VECP arm (40 vs 25%; $P=0.02$) but the estimated 3-year OS showed just a trend favoring this arm (24 vs 13%; $P=0.085$). The VCAP-AMP-VCEP arm was also associated with higher rates of grade 4 neutropenia (98%) and thrombocytopenia (78%), and grade 3 and 4 infections (32%); in fact, three toxic deaths were seen in this arm, two patients died of acute sepsis and one of interstitial pneumonitis. No toxic deaths were seen in the CHOP arm. Of note, in a subset analysis, patients $<56$ years of age derived the longest survival benefit with an estimated 3-year OS at 35%.

*Non-chemotherapeutic options*

Several research groups have evaluated the efficacy of combining IFN-$\alpha$ and zidovudine with mixed results. Although response rates as high as 92% were obtained in some studies, most patients experienced early relapse stressing the need for additional therapy.[17,18] Arsenic trioxide was also used in combination with IFN-$\alpha$ in seven patients with relapsed or refractory ATLL.[19] Despite an initial good overall response rate of 60%, the trial was stopped after 3 weeks due to toxicity ($n=3$) and disease progression ($n=4$).

Basic research has increased our understanding of the biology of ATLL, numerous novel agents, such as denileukin diftitox and alemtuzumab, have been used in patients with ATLL but this experience is limited to case reports.[7,18,20,21] Prospective phase II trials in patients with ATLL evaluating daclizumab (NCT00020020) and denileukin diftitox (NCT00138190) are ongoing. Proteasome inhibitors, antiangiogenic agents, anti-CD40 monoclonal antibodies and RNA interference of Tax are potentially exciting future approaches for the treatment of ATLL.

## Transplantation therapeutic options

In the light of the disappointing results of standard treatments, the role of high-dose treatment in the management of aggressive forms of ATLL has been investigated. Autologous transplantation was rarely attempted and did not yield success.[22] Allogeneic transplantation was first reported in 1987 by Sobue *et al*.[23] After myeloablative conditioning, the recipient received BM graft from a matched sibling and went on to achieve CR only to die on day 205 due to interstitial pneumonitis. It was not until 1996 that Borg *et al*.[5] reported the first successful allogeneic transplant. The recipient was in CR with no evidence of HTLV-1 infection at 23 months post transplant. Several series have since been published all by Japanese groups mainly in form of retrospective series and phase I clinical trials. Although the earlier studies were notable for high incidence of serious infections and other complications, recent experience has been more encouraging.

*Stem cell source*

As discussed further in this study, autologous transplantation in ATLL has rarely been reported and produced rather dismal results. On the other hand, allogeneic transplantation with either related or unrelated donors has yielded more promising results (see below). With regard to the choice of the donor, one concern is the serological status of potential sibling donors. Indeed, at least in the Japanese population, more than two-third of siblings of patients with ATLL are estimated to be HLTV-1 carriers.[3] Whether it is appropriate to use asymptomatic HTLV-1 carriers as donors is unclear at this point. Laws and regulations in the United States as well as the National Marrow Donor program and Foundation for the Accreditation of Cellular Therapy guidelines consider donors with HLTV-1 infection ineligible. Many centers in the United States also exclude such donors altogether. Indeed, there is concern that infusion of HTLV-1-infected stem cell products may lead, in the setting of profound immunosuppression, to the development of donor-driven ATLL. One such case was reported by Tamaki *et al*.[24] However, one may equally argue that the presence of HTLV-1-specific cytotoxic lymphocytes in the graft might be of benefit. There are indeed multiple reports of successful transplantation from HLTV-1-infected but otherwise asymptomatic donors. In a study by Fukushima *et al*.,[25] transplantation from HTLV-1 carriers was associated with improved OS on univariate but not multivariate analysis. Still, higher rate of relapse was noted on multivariate analysis. This issue is even more complicated when G-CSF stem cell mobilization is used. In fact, there is some *in vitro* and *in vivo* data suggesting that G-CSF might promote the growth of ATLL cells.[26] The question of the role of additional testing of presumed asymptomatic HTLV-1 carriers to rule out any sub-clinical ATLL proliferation by review of blood smear, flow cytometry, serum CD25 (IL-2 receptor), proviral load or T-cell receptor gene rearrangement studies remains unanswered. Amidst these concerns, transplantation using unrelated donors has been reported and proved feasible. Although there are no randomized studies comparing related with unrelated donor transplantation in ATLL, both seem to have been equally successful. On the other hand, the experience with umbilical cord blood has been limited and with so far a rather discouraging outcome. In a study by Tanigushi *et al*. (personal communication), 333 patients received reduced-intensity conditioning followed by umbilical cord blood transplantation. The 28 patients with ATLL experienced significantly higher TRM and relapse rate compared with the rest of the group. The calculated 2-year survival was $<20\%$.

*Conditioning regimens*

The earlier studies on allogeneic transplantation for ATLL used mostly myeloablative conditioning regimens, which were predominantly TBI-based.[27] They were noted to have high transplant-related morbidity and mortality. This high toxicity of myeloablative regimens coupled with evidence that ATLL was responsive to graft vs disease effect, lead Okamura *et al*.[28] and Tanosaki *et al*.[29] to perform two consecutive phase I trials using reduced-intensity conditioning. In the ATL-NST-1 and ATL-NST-2 trials patients over the age of 50 received transplants from HLA-matched sibling after conditioning with fludarabine, BU with or without rabbit antithymocyte globulin, respectively. The results of both studies proved that reduced-intensity conditioning is feasible and graft vs disease likely. The best evidence of graft vs disease in ATLL came from a study by Yonekura *et al*.,[30] in which CR was achieved in 6 out of 10 relapsing patients after discontinuation of immunosuppressive therapy. Another remission was obtained in one out of two patients who received donor lymphocyte infusion. To date, there are no published reports of true non-myeloablative strategies.

*Outcome of transplantation*

The transplantation studies published in the English literature, with the exception of case reports, are summarized in Table 1.

There are very limited data on autologous transplantation. Tsukasaki *et al*.[22] reported a single case and found seven other reported cases in the literature. The outcome was grim with disease progression noticed within 10 months in all but one patient who had a remission lasting for 26 months. The patient had been in CR for 10 months before the transplantation. The poor outcome of autologous transplantation might have been related to the disease inherent chemorefractoriness, graft contamination or lack of graft vs disease or graft vs HTLV-1 effect. At any rate, it is reasonable to conclude at this point that autologous transplantation should not be offered to patients with ATLL outside of well-thought clinical trials with innovative approaches and perhaps with focus on antiretroviral strategies.

There is far more experience with allogeneic transplantation. Beside the two small phase I studies, most of the published reports represent rather small retrospective series. When engraftment was reported, it did not seem that there is any delay or lack of engraftment in any of the reported series. This was true regardless of the donor type or HTLV-1 serological status or conditioning regimen intensity. Acute GVHD incidence was within the expected range. Grade II–IV adult GVHD occurred in 47–61% of patients in the largest studies. With the exception of one series reported by Tanosaki *et al*.,[29] in which chronic GVHD developed in 10 out of 12 patients, chronic GVHD did not seem to occur at any higher than anticipated rate. Yet, TRM was in general excessive. In all, 13 out of 40 patients (>30%) experienced TRM within the first 6 months in Fukushima *et al*.[25] series. In Kato *et al*.[31] series, 15% of patients died during the first 20 days and 27% within 100 days. The authors of both series argued that the high mortality was due to the toxicity of the myeloablative nature of the conditioning regimens and profound T-cell deficiency associated with ATLL. Nevertheless, when Tanosaki *et al*.[29] and Okamura *et al*.[28] attempted in their two phase I studies to decrease the incidence of TRM by using reduced-intensity conditioning, they still encountered 10% TRM during the first 100 days and 24% overall. They also reported an incidence of CMV reactivation of 83%. Whether the mortality can be decrease by non-myeloablative approach remains to be determined.

Using Kaplan–Meier method, estimated 3-year OS and relapse-free survival were 45.3 and 33.8%, 49.5 and 49.2%, and 45.3 and 33.8% in Fukushima *et al*.[25] Kato *et al*.[31] and Tanosaki *et al*.[29] and Okamura *et al*.[28] series, respectively. Other studies have shown at least similar outcomes. Indeed a recent heterogeneous series in term of stem cell source and conditioning regimen reported by Shiratori *et al*.,[32] the calculated estimated 3-year OS and relapse-free survival were 73.3 and 66.7%, respectively. Importantly, four out of six patients with recurrent disease achieved partial or CR after decrease or withdrawal of immunosuppressive therapy. In some studies, but not in others factors such as age, disease status at transplantation, and incidence of GVHD had an influence on OS and relapse-free survival.

An interesting observation in some studies was a graft anti-HTLV-1 effect noted with viral clearance after allogeneic transplantation. In the series by Tanosaki *et al*.[29] and Okamura *et al*.,[28] the proviral load was followed serially after transplantation in 13 patients. The value decreased progressively and reached an undetectable level within 6 months in eight patients, including three patients who received HTLV-1-positive grafts. This might be related to the induction and proliferation of $CD8^+$ CTLs specific to selected viral Tax epitopes. Tax is known to accelerate cell growth and inhibit apoptosis promoting oncogenesis. Alternatively, the viral clearance might be due donor-driven CTL in cases where HTLV-1-seropositive donors are used.

*Indications for transplantation*

In the absence of randomized studies comparing anti-tumor chemotherapy to allogeneic transplantation, it is difficult to make any firm recommendation. On the basis of the published experience, it is reasonable, however, to state that as opposed to standard conventional approaches, allogeneic transplantation offers an actual chance of long-term survival to some patients with ATLL. The best approach would be of course to include such patients in clinical trials. In the absence of such trials, physicians must refer patients requiring therapy for evaluation and counseling regarding the option of transplantation. This is in particular true in case of poorly responsive disease or progression after initial non-transplantation treatment.

## Conclusion

In summary, allogeneic transplantation is a feasible option, which seems to offer reasonable chances of long-term survival to some patients with aggressive forms of ATLL.

**Table 1** Summary of published studies on transplantation in ATLL

| *Reference* | N | *Age, years (mean)* | *Gender (F/M; N/N)* | *Subtype (N)* | *Donor type (N)* | *Donor HLTV1 serological status (N)* | *Disease status at diagnosis (N)* | *Stem cell source (N)* | *Acute GVHD prophylaxis (N)* | *Conditioning (N)* | *Median time to neutrophil recovery (days)* | *Acute GVHD % (I and II/III and IV)* | *Chronic GVHD %* | *TRM (N)* | *Median OS* | *Median PFS (%)* | *Relapse rate (%)* | *NRM rate (%)* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Tsukasaki *et al.*[22] | 1 | 33 | F | Acute | Auto | NA | CR | BM | NA | Cy + VP16 + ranimustin | NA | NA | NA | 1 | 14 days | NA | 0 | 100 |
| Ogata *et al.*[37] | 1 | 51 | F | Acute | UD | NA | rD | BM | CSA + MTX | Cy + TBI | 18 | 0 | 100 | 1 | > 16 months | NA | 0 | 0 |
| Tajima *et al.*[38] | 1 | 47 | M | Acute | RD | Negative | rD | BM | CSA + MTX | Cy + MCNU + TBI | NA | 0 | 0 | 0 | > 24 months | NA | 0 | 0 |
| Obama *et al.*[36] | 2 | 38, 33 | 1/1 | Acute (1)<br>Chronic (1) | RD (2) | Positive (1)<br>Negative (1) | CR (2) | BM (2) | CSA + MTX (2) | Cy + TBI | NA | 0 | 100 | 0 | 14 months,<br>> 18 months | NA | 50 | 0 |
| Borg *et al.*[5] | 1 | 41 | F | Acute | RD | Negative | CR | BM | CSA + MTX | Cy + daunorubicin + TBI | 18 | 0 | 0 | 0 | > 23 months | NA | 0 | 0 |
| Yonekura *et al.*[30] | 21 | 37–62 | 13/8 | Acute (18)<br>Lymphoma (2)<br>Chronic (1) | RD (14)<br>UD (7) | NA | CR (7)<br>PR (1)<br>rD (13) | BM (5)<br>PB (14)<br>UCB (2) | CSA + MTX<br>TCR + MTX | NA | NA | 39 (34/5) | NA | 6 | 33.2 ± 10.9<br>at 3 years | NA | 47 | 28 |
| Tanosaki *et al.*[29] | 14 | 50–64 | 9/5 | Acute (10)<br>Lymphoma (4) | RD (14)<br>UD (7) | Positive (7)<br>Negative (7) | CR (4)<br>PR (10) | ND | CSA | Flu + Bu | 11 | 86 (64/22) | 71 | 3 | 36 at 3 years | 31 at 3 years | 43 | 21 |
| Shiratori *et al.*[32] | 15 | 41–66 | 3/12 | Acute (6)<br>Lymphoma (8)<br>Chronic (1) | RD (10)<br>UD (5) | Positive (2)<br>Negative (13) | CR (9)<br>PR (5)<br>rD (1) | BM (8)<br>PB (4)<br>BM + PB (3) | CSA + MTX (11)<br>TCR + MTX (4) | Cy + VP16 + TBI (5)<br>Flu + Bu + TBI (5)<br>Flu + Mel + TBI (5) | 17 | 53 | 66 | 2 | 73.3 at<br>3 years | 67at<br>3 years | 7 | 13 |
| Miyamura *et al.*[34] | 1 | 25 | F | Acute | RD | Positive | PR | PB | CSA + MTX | Cy + TBI | 15 | 0 | 0 | 0 | NA | NA | 0 | 0 |
| Utsunomiya *et al.*[27] | 10 | 33–51 | 7/3 | Acute (8)<br>Lymphoma (1)<br>Other (1)[a] | RD (9)<br>UD (1) | Negative (7)<br>Positive (3) | CR (4)<br>PR (5)<br>rD (1) | BM (8)<br>PB (1)<br>BM + PB (1) | CSA + MTX (9)<br>TCR (1) | TBI | 14 | 60 (40/20) | 40 | 5 | 40 ± 10 at<br>10 years | 17.5 months | 20 | 40 |
| Nakase *et al.*[35] | 8 | 45–59 | 2/6 | Acute (5)<br>Lymphoma (3) | RD (3)<br>UD (5) | Positive (0)<br>Negative (8) | CR (6)<br>rD (2) | ND | CSA + MTX (5)<br>TCR + MTX (3) | Cy + TBI (5)<br>Flu + Bu + TBI (2)<br>Flu + Mel (1) | NA | 87 (87/0 | 37 | 3 | 20 months | 16.5 months | 12 | 25 |
| Kami *et al.*[33] | 11 | 15–59 | 7/4 | Acute (5)<br>Lymphoma (4)<br>Chronic (2) | RD (10)<br>UD (1) | Negative (9)<br>Positive (2) | CR (6)<br>PR (1)<br>rD (4) | BM (7)<br>PB (3)<br>BM + PB (1) | CSA + MTX | TBI based (8)<br>Cy + Bu (1)<br>Flu + Cy ± ATG (2) | 11 | 45 | 27 | 7 | 54.5 ± 30<br>at 1 year | 45 ± 30 at<br>1 year | 0 | 64 |
| Fukushima *et al.*[29] | 40 | 28–53 | 22/18 | Acute (30)<br>Lymphoma (10) | RD (32)<br>UD (8) | Negative (27)<br>Positive (9)<br>ND (4) | CR (15)<br>PR (13)<br>rD (12) | BM (21)<br>PB (19) | CSA + MTX (28)<br>TCR + MTX (11)<br>TCR (1) | TBI based (22)<br>Bu based (17)<br>Mel based (1) | 15 | 65 (48/17) | 37 | 17 | 45.3<br>(31.8–58.8)<br>at 3 years | 33.8<br>(17.2–49.4)<br>at 3 years | 25 | 42 |
| Kato *et al.*[31] | 33 | 24–59 | 18/15 | Acute (20)<br>Lymphoma (7)<br>ND (6) | UD (33) | Negative (33)<br>Positive (0) | CR + PR (15)<br>rD (14)<br>ND (4) | BM (33) | CSA + MTX (13)<br>TCR + MTX (20) | TBI based (22) | NA | 76 (61/15) | 12 | 9[a] | 49.5<br>(31.2–78.5)<br>at 1 year | 49.2<br>(33.6–72.1)<br>at 1 year | 15 | 27 |
| Okamura *et al.*[28] | 16 | 51–67 | 9/7 | Acute (11)<br>Lymphoma (5) | RD (16) | Negative (8)<br>Positive (8) | CR (3)<br>PR (10)<br>RD (3) | PB (16) | CSA | Flu + Bu + ATG | NA | 63 (31/32) | 37 | 4 | 33.3 ± 12.2<br>at 5 years | 20 ± 10.3<br>at 2 years | 56 | 25 |
| Sobue *et al.*[23] | 1 | 43 | M | Acute | RD | Negative | rD | BM | MTX | Cy + TBI | 20 | 0 | 0 | 1 | 7 | NA | 0 | 100 |

Abbreviations: F = female; HTLV-1 = human T-cell lymphotropic virus type 1; M = male; Mel = melphalan; NA = not available; NRM = non-relapse mortality; PB = peripheral blood; RD = related donor; rD = recurrent disease; TCR = tacrolimus; UD = unrelated donor; VP16 = etoposide.
[a]Cause of death unknown in three cases.

However, one must be cautious in extrapolating data from the Japanese literature to allogeneic transplantation given the lesser degree of population diversity. In addition to establishing the true role of transplantation in treatment of ATLL, numerous questions remain also unanswered with regard to donor selection, role of retroviral and other adjunct therapies, intensity of conditioning, and role of proviral load monitoring. In a disease that still carries a grim prognosis, there is ample opportunity for clinical research. The rarity of the disease and its specific epidemiological distribution calls for international collaboration.

## Conflict of interest

The authors declare no conflict of interest.

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