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REVIEW

Striving to cure adult T-cell leukaemia/lymphoma: a role for allogeneic stem cell transplant?

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Adult T-cell leukaemia/lymphoma (ATL) is an aggressive HTLV-1-related malignancy, rare outside of regions where the retrovirus is endemic. Although the use of antiviral therapy has improved outcomes, particularly for indolent forms of ATL, response to combination chemotherapy is poor and outcomes for aggressive subtypes remains dismal. Consolidation with allogeneic stem cell transplant (alloSCT) has an increasing role in the management of ATL in eligible patients, offering favourable long-term remission rates. However, relatively high-transplant-related mortality and issues with donor recruitment for certain ethnicities remain problematic. In this review, we discuss the rationale for and issues surrounding alloSCT in ATL in the context of conventional and emerging therapies.

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INTRODUCTION

Adult T-cell leukaemia/lymphoma (ATL) is a rare but aggressive peripheral T-cell lymphoma causally linked to infection with the retrovirus human T-lymphotropic virus-1 (HTLV-1).[1] ATL is usually diagnosed in individuals from areas of HTLV-1 endemicity including Japan, the Caribbean, South America, West Africa, Melanesia and the Middle East. Between 3 and 5% of HTLV-1-infected individuals develop ATL with onset most frequent in the 5th–6th decade.[2,3] In Western countries peripheral T-cell lymphoma accounts for 5–10% of all non-Hodgkin's lymphoma, with ATL comprising just 1–2% of cases, whereas in Asia peripheral T-cell lymphoma comprises 15–20% of non-Hodgkin's lymphoma cases, of which ~25% are ATL, particularly in Japan.[4,5]

ATL is classified according to the Shimoyama classification,[6] comprising four subtypes with widely differing 4-year survival rates: smouldering (52%), chronic (36%), lymphomatous (16%) and acute (11%).[7] Other major prognostic factors include advanced performance status, high lactate dehydrogenase, age $\geqslant 40$ years and hypercalcaemia.[8] Molecular aberrations associated with poor prognosis include mutation or deletion of the tumour suppressor genes p53[9,10] and p15/16.[10,11]

Lymphoma is the most frequent indication for haemopoietic stem cell transplantation in Europe.[12] While the majority are autologous haemopoietic stem cell transplants (autoSCT), use of allogeneic haemopoietic stem cell transplantation (alloSCT) has increased, particularly since the advent of reduced intensity (RI) conditioning protocols. In aggressive forms of ATL, there is increasing evidence for alloSCT but the relatively high-transplant-related mortality (TRM) remains problematic. Given the rarity of ATL, there are very few randomised, prospective trials to guide management. Most of the evidence in favour of alloSCT is based on data from large Japanese transplant registry studies, whilst experience outside of endemic areas is relatively limited. This review focuses on published data regarding the role primarily of alloSCT in ATL and outlines its use in the context of currently available treatment modalities.

FIRST-LINE TREATMENT: CHEMOTHERAPY AND ANTIVIRAL THERAPY

Complex dose intense combination chemotherapy improves response rates and PFS, but so far a significant impact on overall survival (OS) has not been demonstrated with any individual regimen.[13,14] Factors that potentially account for this include intrinsic drug resistance secondary to p53 dysfunction[15] or overexpression of multi-drug resistance proteins,[16,17] an older patient population with comorbidities, and frequent opportunistic infections due to acquired cellular immunodeficiency associated with HTLV-I infection. Response rates above 70% have been reported with the intensive multi-drug regimen mLSG15,[13,14,18] which were superior to CHOP-14 in a randomised phase 3 study.[13] However, a trend towards improved OS did not reach statistical significance (24 vs 13%, respectively, two-sided $P=0.169$).[13] ATL lymphoma patients seem to benefit more from this dose intense regimen, whereas for acute ATL, CR rates with LSG15 are below 20% and 4-year OS is $<15\%$.[14] Intrathecal chemotherapy is recommended with acute/lymphoma subtypes to prevent frequent meningeal relapse.[19]

The efficacy of antiviral therapy (AVT) with zidovudine and interferon-alpha (IFN-α) has been demonstrated in multiple studies.[20–24] It is particularly effective in chronic and smouldering ATL, with 100% 5-year survival in an international meta-analysis ($n=17$).[20] In acute ATL, both first-line and maintenance AVT significantly improved OS over chemotherapy alone. Outcomes, however, remained poor with a median OS of 6 months and 5-year OS of 15% for the whole cohort and 28% for patients treated with AVT alone. In lymphomatous ATL, first-line treatment with AVT alone resulted in a significant survival disadvantage compared with chemotherapy;[20] best results were obtained with chemotherapy combined with AVT.[24]

The efficacy of novel agents including arsenic trioxide,[25,26] Lenalidomide,[27] Bortezomib[28–30] and monoclonal antibodies against CCR4 (Mogamulizumab),[18,31] CD25 (Daclizumab),[32,33] CD52 (Alemtuzumab)[34,35] and CD30 are being explored but these

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treatments remain experimental for the most part. The combination of arsenic trioxide and AVT is effective and induces rapid and prolonged responses in chronic ATL.[25,36] Promising results are reported in lymphoma/acute ATL with combined arsenic trioxide/IFN-α consolidation following chemotherapy or AVT to eradicate minimal residual disease (reference 37 and O. Hermine, unpublished data). Single agent Mogamulizumab has shown promise with an overall response rate of 50% and median OS of 13.7 months in relapsed aggressive ATL.[31] The potential of immunochemotherapy was explored in a randomised phase 2 trial; the addition of Mogamulizumab to combination chemotherapy improved response rates, albeit with increased toxicity and survival data are immature.[18]

The prognosis of aggressive ATL subtypes remains dismal with a median survival of < 12 months.[7,20] Some groups have attempted to define cohorts of patients that may fare well with current therapies. For a proportion of acute ATL patients achieving CR with AVT alone (29.7%), 5-year OS was 82%.[20] Kawada *et al.*[38] reported a 3-year OS of 61.5% with chemotherapy alone for 15 patients with serum soluble IL-2 receptor (s-IL2R) levels < 2000 iU/mL for over 3 months. However, it is clear that current treatment regimens are suboptimal for the majority of patients with aggressive ATL, and therefore many groups have adopted transplant strategies as consolidation to improve survival rates in eligible patients.

AUTOLOGOUS HAEMATOPOIETIC STEM CELL TRANSPLANTATION

Published data on autoSCT is limited to retrospective case reports or series. Owing to the variety of chemotherapy regimens used for induction, conditioning and, in some cases, post autoSCT consolidation, it is difficult to derive meaningful data but outcomes have generally been poor. The largest Japanese series to date reports eight cases of autoSCT for ATL, all of whom relapsed or died of transplant complications, with a median remission of only 3.5 months.[39] In an American case series, all four relapsed ATL patients progressed within 18 months of autoSCT.[40] An additional four cases of autoSCT were recently reported by the European Society for Blood and Marrow Transplantation (EBMT) Registry, all of whom died within 1 year.[41] No published data on the use of AVT in conjunction with autoSCT exist. Two case reports suggest efficacy may be improved if IFN-α therapy is commenced following autoSCT.[42,43] Ongoing remission at 26 months with IFN-α maintenance represents the longest reported remission post autoSCT.[42] Given the rarity of sustained remissions, there is no discernible benefit of autoSCT consolidation.

ALLOGENEIC HAEMATOPOIETIC STEM CELL TRANSPLANTATION

AlloSCT offers a range of potential benefits over autoSCT. First, there is no potential for graft contamination by ATL. Second, there is the potential for development of a graft-vs-ATL (GvL) response to control or eliminate residual disease. Third, long-term remissions have been reported in approximately a third of alloSCT recipients,[44–46] which, in a proportion, is likely to be synonymous with cure. This is offset, however, against an increased TRM, requiring careful donor and patient selection, taking into consideration age and co-morbidities.

There has been no randomised comparison of chemotherapy alone vs alloSCT consolidation. A single centre retrospective study showed improved 3-year OS in alloSCT recipients ($n = 29$) over those receiving chemotherapy alone ($n = 37$; 44.9 vs 27.7% $P < 0.05$).[38] Baseline characteristics of alloSCT and non-SCT groups appear similar but selection bias is an inherent issue.[38] The largest retrospective analysis of alloSCT in Japan included outcome data on 578 patients with ATL transplanted between February 1992 and December 2009.[47] Three-year OS was 36% with a median OS of 9–10 months and TRM of 34%.

Most reports are derived from retrospective analyses of Japanese Registry Data. This represents a population less genetically diverse than other countries where ATL is prevalent. GvHD rates may be lower in Japanese compared with Western populations through reduced HLA diversity.[48] Thus direct translation of these results to other ethnic groups must be with caution. The EBMT registry recently reported 3-year OS rates of 34.3% in a cohort of 17 ATL patients,[41] demonstrating that alloSCT is a feasible strategy outside of Japan.

RECIPIENT FACTORS

Male sex, increased age (> 50 years) and reduced performance status have been consistently associated with inferior outcomes.[44,47,49] Better outcomes are achieved when transplanted in first clinical remission[7] and, for related donors, when transplanted early in the disease course (< 100 days after diagnosis).[50] Failure to achieve CR before alloSCT also correlates with worse outcomes, although long-term remission can still be achieved in a small proportion of patients. A Japanese registry study ($n = 386$) reported a survival probability of 26% in patients failing to achieve CR vs 51% for those transplanted in first CR.[44] Several small retrospective studies suggest high sIL-2R levels prior to transplant predict adverse OS on univariate analysis,[38,51] presumably as a surrogate marker for ATL burden. No clear impact of ATL subtype on outcome following alloSCT has been demonstrated.[49]

DONOR SELECTION

Given the rapidly progressive nature of ATL, consideration of alloSCT should commence early in disease management to minimise delay. Table 1 outlines results from the largest prospective and retrospective trials according to donor source.

Sibling donors are preferred due to donor accessibility and superior outcomes, although in Japan only one in three ATL patients have a matched sibling donor, of whom two-thirds are HTLV-1 carriers.[54] A retrospective study of 113 patients achieving CR post-alloSCT suggests higher disease-related mortality with HTLV-1-positive donors on multivariate analysis, but ultimately no difference in OS.[44] There are two reports of donor-derived ATL arising 4 months[55] and 9 years[56] post alloSCT from HTLV-1-positive siblings. Thus, HTLV-1 seronegative donors are often preferred, although there is little evidence to support this at present.

In Japan, a suitable unrelated donor will be found in one-third of cases. In Europe and America, where most patients with ATL are of African or African-American descent, donors of similar ethnic origin continue to be under-represented in donor registries. In the UK, African/Afro-Caribbean donors accounted for only 2.4% of donors of known ethnic origin.[57]

Early reports of unrelated donor alloSCT were unfavourable. None of the 15 recipients in an early study survived > 500 days.[58] Since then, multiple studies have demonstrated the efficacy of using unrelated donors in ATL.[44,59,60] A recent analysis demonstrated significantly inferior OS with unrelated donors ($n = 306$) compared with HLA-matched siblings ($n = 210$), although the frequency of HLA mismatch in the unrelated group was not stated.[47] Reports on alloSCT with partially matched related donors suggest feasibility, although outcome may be inferior (Table 1).[44,47]

Very few data exist on the use of haploidentical donors in ATL specifically. In one study, three patients with refractory ATL received haploidentical sibling alloSCT matched for non-inherited maternal antigens. One patient died of GvHD while the others relapsed.[61] Although small numbers of haploidentical transplants have been included in larger series,[41,44] outcomes for these

Table 1. Outcomes of prospective and major retrospective trials in alloSCT for aggressive ATL, focussing on donor source and pre-transplant conditioning

References	*Nature of study*	n	*Median age (years)*	CR *pre-alloSCT (%)*	*Donor*	*Conditioning*	*TRM (%)*	*Disease-related mortality (%)*	*Median OS (months)*	*3-year OS (%)*	*HR for OS*
Okamura *et al.* (2005)[52]	Prospective	16	57	20	Sib FM	RIC	25	40	NS	31 (2-year OS)	–
Tanosaki *et al.* (2008)[53]	Prospective	14	56	29	Sib FM	RIC	21.4	36	NS	33	–
Hishizawa *et al.* (2010)[44]	Retrospective	154	(47% >50 years)	16	Sib FM	NA	37	21	9.8	41	1
		43	(60% >50 years)	35	Sib MM		43	32	2.5	24	1.55
		99	(45% >50 years)	29	Unrelated		42	19	9.6	39	1.24
		90	(72% >50 years)	35	Single-unit UCBT		52	30	2.6	17	2.08**
Ishida *et al.* (2012)[47]	Retrospective	586	53	38		48% MA	34	26	9.9	36	
		210			Sib FM						1
		62			Sib MM						1.30
		306			Unrelated						1.28**
		280	49	34	34% Sib FM	MA	36.5	22.2	9.5	39	1
		306	57	37	38% Sib FM	RIC	31.9	30.9*	10	34	1.087
Bazarbachi *et al.* (2014)[41]	Retrospective	17	47	53	35% Sib FM	24% MA	17.6	47	NS	34	

Abbreviations: alloSCT = allogeneic haemopoietic stem cell transplantation; ATL = adult T-cell leukaemia/lymphoma; FM = fully HLA-matched; HR = hazard ratio; MA = myeloablative; MM = partial HLA mismatch; NA = not available; OS = overall survival; RIC = reduced intensity conditioning; Sib = sibling; TRM = transplant-related mortality; UCBT = umbilical cord blood transplantation. *$P < 0.05$ compared with MA conditioning. **$P < 0.05$ compared with FM sib alloSCT.

patients have not been individually reported. Major concerns include higher TRM,[62] although recent data suggest reasonable outcomes with newer protocols for haploidentical alloSCT in other haematological malignancies, including older patient cohorts.[63,64] This approach remains experimental in ATL.

UMBILICAL CORD BLOOD TRANSPLANTATION (UCBT)

Durable remissions have been achieved with single and double-unit UCBT.[44,65,66] A major benefit is the rapid access to donor units. Rates of GvHD are lower than with unrelated donors, allowing use of partially HLA-mismatched units; although this may potentially compromise a GvL effect. Furthermore, donor lymphocyte infusion is not an option for relapse post-alloSCT.

A retrospective analysis of single-unit UCBT in ATL ($n = 90$) demonstrated inferior outcomes with high rates of graft failure (17%, median CD34+ cell dose 2.55×10^7) and high TRM (51%), although ATL-related mortality was similar to other donor sources. Median OS was just 2.6 months with 3-year OS of 17%.[44] Patient selection and disease status at SCT are crucial; a retrospective analysis of 27 ATL patients receiving UCBT reported 3-year OS of 50% for 16 patients achieving at least partial response pre-alloSCT, but only 9.1% for those with chemorefractory disease.[67] Little is known about the comparative efficacy of double-unit UCBT in ATL, which might reduce the high TRM by reducing graft failure rates and hastening count recovery. Given that UCBT in other mature lymphoid neoplasms can achieve outcomes similar to unrelated donor alloSCT,[68] its role warrants further exploration but optimisation of UCBT protocols is required before routine use in ATL.

CONDITIONING REGIMENS

Given that HTLV-1-related ATL has a long latency with a median presentation of over 60 years of age, RI regimens are increasingly used. Myeloablative (MA) alloSCT regimens, although feasible in younger recipients, are now less commonly performed. RI conditioning regimens have less cytotoxic potential, therefore alloSCT is more reliant on GvL effect. The feasibility of RI regimens in older patients (50–67 years) was demonstrated in two prospective trials.[52,53] Importantly, a large Japanese retrospective study of 586 alloSCT recipients demonstrated no difference in OS between MA and RI conditioning on multivariate analysis,[47] although suggestive of a trend towards improved OS with RI conditioning in patients aged 56–72 years ($P = 0.072$; Table 1). Although TRM was marginally higher in MA alloSCT patients, this did not reach statistical significance; whereas ATL-related mortality was significantly higher in RI over MA alloSCT (hazard ratio 1.579 $P = 0.019$).[47]

No prospective comparison of conditioning regimens has been undertaken. Japanese data suggest that fludarabine-based conditioning regimens in combination with melphalan for RI alloSCT are superior to those incorporating busulphan (hazard ratio for OS 0.645, $P = 0.015$). For MA alloSCT, TBI, melphalan and busulphan-based regimens have all been used, with no clear difference in outcomes.[47]

The role of *in vivo* T-cell depletion with ATG or alemtuzumab has not been fully explored; most Japanese patients receive T-replete transplants.[44] Alemtuzumab has shown some efficacy in ATL outside of the transplant setting,[34,35] but could also risk suppressing an early GvL effect in a rapidly relapsing malignancy. A high rate of early relapse was noted in a phase 1 study incorporating low dose ATG (5mg/kg) with fludarabine/busulphan conditioning.[52] However, a follow-on study omitting ATG demonstrated similar survival rates without an increase in GvHD, although numbers were small.[53]

The G-CSF receptor is expressed on ATL cells, with evidence of G-CSF-induced ATL proliferation in a small proportion of patients, leading to theoretical concern that G-CSF administration may promote disease progression.[69,70] Whether this correlates with clinical outcomes, however, is unclear.

INFECTIVE COMPLICATIONS

TRM and infectious complications are relatively high in ATL patients, partly attributable to HTLV-1-mediated immunodeficiency. A recent study reported 1-year infection-related mortality of 14.7% in ATL patients post alloSCT ($n = 68$), which was higher than in acute myeloid and acute lymphoblastic leukaemia patients (6.1% and 2.0%, respectively) on univariate analysis only, and attributable to a range of bacterial, viral and fungal pathogens.[71] CMV infection, assessed by pp65 antigen detection, was associated with inferior OS on multivariate analysis in ATL only.[71]

IMMUNE RECONSTITUTION: GVH VS GVL EFFECT

The association of GvHD with rates of long-term remission implies the presence of a GvL effect.[46,59] A retrospective study of alloSCT in 616 Japanese ATL patients showed improved OS in patients with both limited acute GvHD (grades I–II) and extensive chronic GvHD compared with patients without GvHD. There was also a trend towards improved OS in those limited stage chronic GvHD. Severe acute GvHD (grades III–IV) was associated with inferior OS.[49]

The observation that some ATL relapses can be successfully managed with a withdrawal of immunosuppression supports the presence of a GvL effect.[52,53,72,73] In a recent retrospective study, 2 out of 29 patients with relapsed ATL post alloSCT achieved CR with withdrawal of immunosuppression alone, both in association with emergence of GvHD.[74] Long-term remissions have been reported with donor lymphocyte infusion, in all cases associated with exacerbation of GvHD.[74,75] Five of nine patients responded clinically to donor lymphocyte infusion, three of whom achieved a durable CR (>3 years).[74] Conventional chemotherapy alone was ineffective in all cases of systemic relapse in this study.[74]

Vigorous HTLV-1-specific cytotoxic T lymphocyte (CTL) responses have been demonstrated in ATL patients following alloSCT, which were not detectable pre-transplant.[76,77] These CTLs are cytotoxic to ATL cells in *in vitro* and animal studies.[78,79] Multiple HTLV-1-related epitopes have been identified as targets including the retroviral Tax protein,[76,78,80] and basic leucine zipper factor.[77,81] One study identified Tax-specific T-cell responses in 68.8% of alloSCT recipients ($n=16$), all of whom had 100% donor chimerism.[82] HTLV-1-specific CTLs can persist in long-term survivors[83] and a small study ($n<5$) has suggested this may correlate with ongoing ATL remission.[76] Recently, Tax-specific CD4+ T cells were identified in ATL patients post alloSCT, which were shown to augment CD8+ CTL expansion and are likely to contribute to a GvL effect.[82]

HTLV-1-specific proteins are attractive and specific targets for potential immunotherapy. Modified T-cells expressing receptors targeting HTLV-1-specific epitopes have been developed against both human telomerase reverse transcriptase[84] and Tax[79] with some evidence of ATL response in preclinical studies.[79,84] Recombinant vaccinia virus-based vaccines expressing basic leucine zipper peptides have also shown preclinical efficacy.[81]

In addition to direct anti-ATL effects, Mogamulizumab suppresses regulatory T-cell function, theoretically enhancing a GvL response in post-alloSCT relapse, although its efficacy in this setting is confined to a single case report.[85] However, there is also concern that mogamulizumab, particularly when administered pre-transplant, may increase acute GvH and non-relapse mortality.[86,87] Enhancing the GvL response whilst minimising GvH is problematic, as with all haematological malignancies, but at present there is no evidence to suggest use of specific GvH prophylaxis strategies, or pre-emptive donor lymphocyte infusion, in ATL patients.

HTLV-1, MINIMAL RESIDUAL DISEASE AND MAINTENANCE THERAPY

Development of non-malignant HTLV-1-mediated disease is a potential concern following post-alloSCT immunosuppression but is confined to a single case report of HTLV-1 encephalitis[88] and a postulated case of HTLV-1-associated myelopathy.[89] There are multiple reports of acute HTLV-1 complications following solid organ transplantation from HTLV-1-positive donors.[90] In a recent study, reporting the kinetics of early HTLV-1 infection in three recipients of solid organ transplants from HTLV-1-positive donors, infection disseminated rapidly despite early AVT, peaking at 6 weeks post transplant with early clonal expansion. The extent to which pre-existing anti-HTLV-1 immune responses mitigate this in ATL patients has not been fully explored.

The ability of alloSCT to eradicate HTLV-1 is well documented.[46,91–93] HTLV-1 eradication, however, is not essential; a proportion of long-term survivors maintain stable proviral loads at pre-alloSCT levels.[46] Recurrence of HTLV-1 may herald disease relapse,[72] but may also represent *de novo* infection of donor lymphocytes, where patients in ongoing remission have shown reemergence of HTLV-1 despite maintaining full donor chimerism.[46,53,72,94] Analysis of HTLV-1 provirus insertion sites can assess HTLV-1 clonality[95,96] and might allow detection of emergent clones with the same insertion site as the original ATL clone as an minimal residual disease marker, although its use in this context is not validated. In theory, using AVT following alloSCT may prevent infection of donor T-cells in an immune-compromised environment; we have observed a reduction in proviral loads after AVT in one patient (O Hermine, unpublished data). However, there are very few data to validate the use of AVT, or any other maintenance therapy, in the post-alloSCT setting to date. The role of HTLV-1 monitoring and AVT post-alloSCT warrants further investigation but is uncertain at present.

CONCLUSION

AlloSCT consolidation has a pivotal role in managing aggressive ATL. However, it is important to note that outcomes, in general, have only marginally improved over recent decades with a minority ($<20\%$) of acute/lymphoma ATL patients receiving alloSCT,[7,24] presumably due to donor availability, patient comorbidities/age or disease behaviour. To widen access, improved donor recruitment from relevant ethnic groups and research into optimising outcomes with mismatched or UCB donors is needed. Outcomes for treatment-refractory patients remain extremely poor, regardless of treatment strategy, and research into novel agents and immunotherapy is crucial. Currently alloSCT is the preferred option where feasible but more information on prognostic factors and outcomes, with and without alloSCT consolidation, will help to select those who will derive the most benefit from alloSCT in future.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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