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Mogamulizumab *versus* investigator choice in relapsed/refractory adult T-cell leukemia/lymphoma: all four one or none for all?

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The human T-cell lymphotropic (or leukemia) virus type-1 (HTLV-1) was isolated by Poiesz *et al.* in 1980 from the T-cell line Hut-102, established from a patient thought to have cutaneous T-cell lymphoma.[1] HTLV-1 causes adult T-cell leukemia/lymphoma (ATL), HTLV-1 associated myelopathy/tropical spastic paresis (HAM/TSP), and other inflammatory disorders.[2] ATL is a clinically heterogeneous but often very aggressive mature T-cell neoplasm with dismal survival rates and limited therapeutic options, particularly in the relapsed/refractory (R/R) setting.[3] Most cohort studies and clinical trials in ATL come from Japan where the virus is highly endemic in certain regions. Here, investigators have led efforts to define diagnostic criteria, clinical subtypes, prognostic models, and the value of new therapies, including the anti-CCR4 antibody mogamulizumab (KW-0761), approved in Japan for both R/R and chemotherapy-naïve CCR4-positive ATL.[4,5] Data on subtype frequency, natural history, and outcome in ATL from non-Japanese endemic regions and from non-endemic regions (North America, Europe) remain very limited, although recent studies have begun to shed some light on this, showing that North American ATL patients present with more aggressive disease and have a worse prognosis (median survival approx. 7 months) compared to Japanese patients.[6,7] The availability of mogamulizumab for ATL in Japan provided the impetus to explore its activity in other ATL populations. In this issue of *Haematologica*, an important study by Phillips *et al.*[8] significantly advances our understanding of the global therapeutic impact of mogamulizumab in ATL, by reporting results of an international randomized Phase II trial (KW-0761-009) assessing the safety and efficacy of mogamulizumab *versus* investigator choice of chemotherapy in patients with R/R ATL.

HTLV-1 belongs to a group of T-lymphotropic deltaretroviruses, which includes four types of Simian T-lymphotropic viruses (STLV). HTLV-1 is believed to have originated from interspecies transmission between STLV-1-infected Old-World monkeys and humans. HTLV-1 is highly endemic in Southwestern Japan, the Caribbean, Northern Iran, and in Aboriginal populations in central Australia.[9] HTLV-1 RNA is reverse-transcribed into a

double-stranded DNA that integrates into the host cell genome as a provirus. The proviral dsDNA is marked at both ends by long terminal repeats (LTRs), which serve as promoters for sense (5'-LTR) and antisense (3'-LTR) transcription.[10] Two key oncogenic proteins, Tax and HBZ (HTLV-1 basic leucine zipper factor) (Figure 1), are encoded in the pX region in the 3' end of the provirus.

An estimated 10-15 million people worldwide are infected with HTLV-1.[9] The virus is transmitted vertically (breast milk) and horizontally (sexual contact, blood products), infecting primarily mature CD4^{+} T cells with a CD25^{+}FOXP3^{+} regulatory T-cell (T_reg) phenotype.[11] Direct
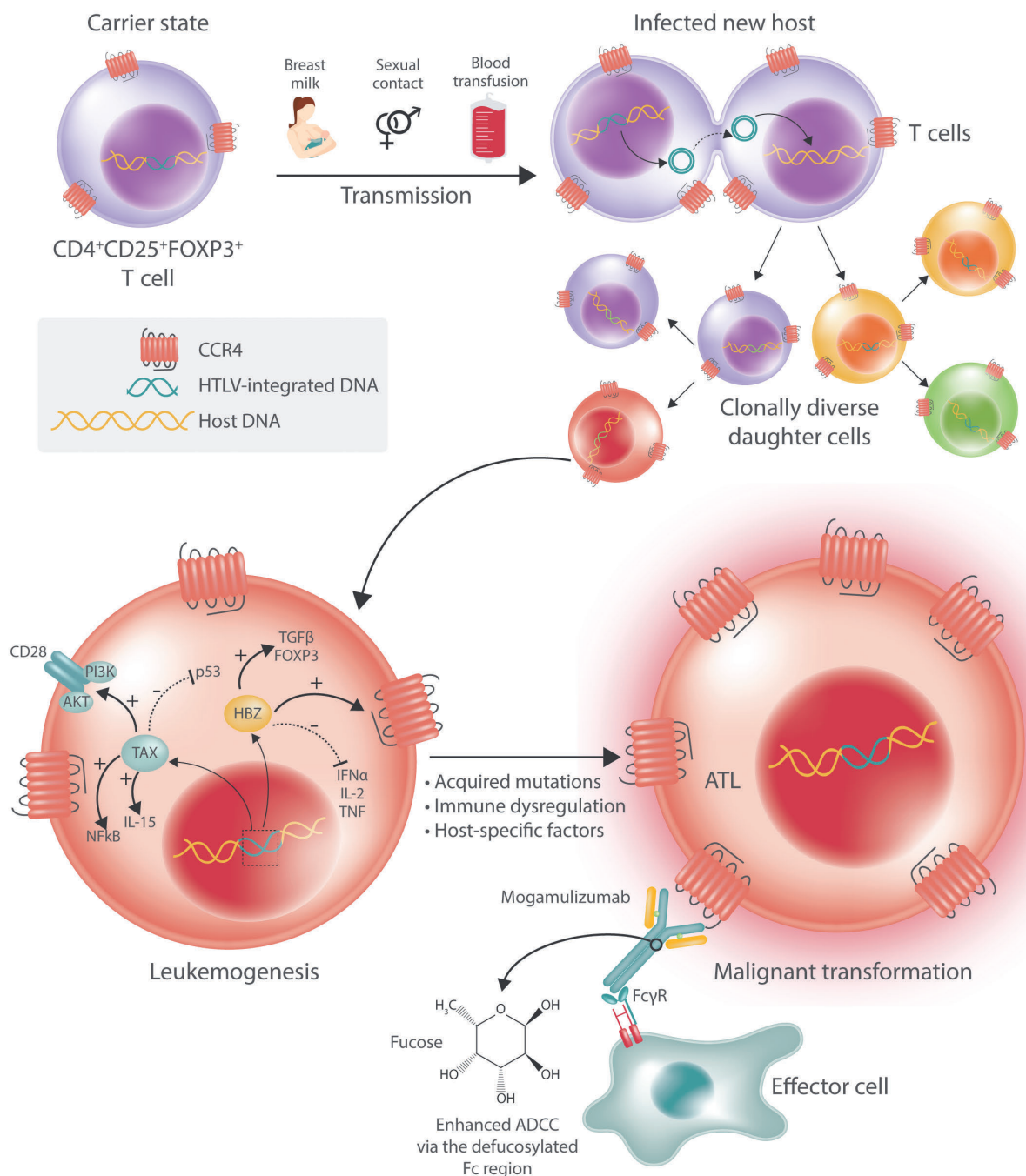
Figure 1. Transmission, replication, and oncogenesis of HTLV-1 in adult T-cell leukemia/lymphoma (ATL). Transmission of infected CD4^{+}CD25^{+}FOXP3^{+} cells occurs *via* vertical and horizontal routes to a new host. Reverse transcribed HTLV-1 DNA is integrated into the DNA of host cells. and direct cell-to-cell contact and mitosis drives viral replication leading to a clonally diverse population of infected cells. Two transcription regulators, Tax and the HTLV-I basic leucine zipper factor (HBZ) are essential for oncogenesis. Tax up-regulates the P13K/AkT and NFκB pathways including through IL-15, and down-regulates p53. HBZ up-regulates TGFβ, FOXP3, and the C-C chemokine receptor 4 (CCR4) while down-regulating INFα, IL-2, and TNF. After decades of complex interactions between these molecules, together with the acquisition of new mutations, immune dysregulation, and host-specific factors, ATL develops in 2-5% of carriers. The defucosylated monoclonal antibody mogamulizumab binds CCR4 leading to enhanced antibody-dependent cellular cytotoxicity (ADCC).

cell-to-cell contact is necessary for the infection of new T cells, while the expansion of the HTLV-1 proviral load is achieved by proliferation of infected T cells, which leads to a clonally diverse neoplastic population[11] (Figure 1).

Extensive molecular aberrations in HTLV-1-infected T cells, often accumulating over decades, lead to the development of ATL in approximately 3-5% of seropositive carriers. HTLV-1 induced leukemogenesis is a complex, multistep process, driven by Tax and HBZ. Tax-induced upregulation of IL-15, IL-15Rα, and EZH-2 leads to chronic inflammation and polycomb repressive complex 2 (PRC2) hyperactivation, with genome-wide H3K27me3 accumulation.[12] Expression of HBZ by HTLV-1 infected T cells results in increased proliferation, impaired apoptosis, and disruption of genomic integrity.[13] Analysis of the somatic mutation landscape of ATL reveals common mutations at *TP53* and *IRF4*, and copy number alterations at PD-L1 and CDKN2A.[14]

HTLV-1 seroprevalence rates mean that ATL predominates in endemic regions, accounting for up to 35% of all T-cell lymphomas in endemic areas in Japan and 15-20% in Peru. However, these figures are only 1-2% in North America and Europe.[15] ATL can present with four clinical subtypes: acute, lymphomatous, chronic, and smoldering. A consensus report highlighting the clinical features and treatment guidelines of these subtypes (including an increasingly appreciated fifth subtype: aggressive extranodal primary cutaneous) was recently updated.[16]

Retrospective studies have described significant clinical and biological differences between Japanese ATL and North American ATL, including a slight female predominance, a younger median age at diagnosis (61-67 *vs.* 50-54 years), and a higher frequency of aggressive subtypes (acute and lymphomatous) (approx. 75% *vs.* 88-94%).[6,7] There are also differences in the mutational landscape, with significantly higher mutation rates for epigenetic regulators, and fewer T-cell receptor/NF-κB pathway alterations in North American ATL compared to Japanese ATL.[17]

Despite advances in our understanding of the biology of HTLV-1 and ATL, prognosis remains very poor, with median overall survival (OS) of 8.3 months (acute), 10.6 months (lymphomatous), 31.5 months (chronic), and 55 months (smoldering);[18] western ATL patients may have a worse prognosis.[6,7] Treatment strategies differ significantly between endemic and non-endemic regions. In Japan, the LSG15 regimen was superior to CHOP-14, with higher complete remission (CR) rate and a trend towards improved 3-year OS (24% *vs.* 13%).[19] However, this regimen is not routinely used outside Japan, and the most frequently used chemotherapies in North American ATL are CHOP-like regimens, with overall response rates (ORR) of approximately 60-75% and CR rates of 13-36%.[6,7] Consolidation with allogeneic hematopoietic stem cell transplantation (HSCT) is generally recommended for eligible patients with aggressive ATL subtypes, with Japanese studies showing 3-4 year OS ranging between 26% and 36%.[20]

Unfortunately, most ATL patients relapse, and multiagent salvage chemotherapy is generally ineffective.[18] The discovery that C-C chemokine receptor 4 (CCR4) is expressed in over 90% of ATL cases, led to the clinical development of mogamulizumab, a glycoengineered anti-CCR4 monoclonal antibody with a defucosylated Fc region that enhances ADCC. In 2012, mogamulizumab was approved for ATL in Japan in the relapsed setting on the basis of a Phase II trial that showed a 50% ORR,[4] and in 2014 was approved for chemotherapy-naïve patients, based on a randomized Phase II trial in combination with the mLSG15 regimen.[5] Both studies were quite small (28 and 53 patients, respectively) with ORR as the primary end point. Up-dated outcomes analyses appear to show a real, but relatively modest, benefit for mogamulizumab, with median PFS and OS of 5.2 and 14.4 months for the single arm R/R ATL cohort and 1-year progression-free survival (PFS) 47% and 29% for mLSG15 + mogamulizumab *versus* mLSG15 in the randomized front-line study.[21]

In this context, the study by Phillips *et al.*[8] aimed to determine if the incremental, but encouraging, outcome improvements with mogamulizumab in Japanese ATL could be replicated in non-Japanese ATL. This international Phase II study, conducted at 22 centers, randomized (2:1 ratio) 71 patients with R/R ATL with at least one prior line of therapy to either mogamulizumab (n=47) or investigator choice chemotherapy (n=24: GemOx=21; pralatrexate=2; DHAP=1). The primary objective of the study was confirmed overall response rate (cORR), defined as a response sustained for ≥8 weeks. In the mogamulizumab arm, cORRs by investigator and independent review were 15% and 11%, respectively, notably inferior to that of the Japanese registration study.[3] Remarkably, the cORR in the investigator's choice arm was 0%. Concordant with the Japanese Phase II study, the best responses to mogamulizumab by compartment were in blood (54%, all CR) and skin (44%), with no CR in lymph nodes. Responses were observed in all clinical subtypes.

Given the study design, with 18 out of 24 patients (75%) on the investigator choice arm crossing over to the investigational arm, it was not possible to assess any OS benefit from mogamulizumab. Median PFS was poor in each arm (0.93 months for mogamulizumab *vs.* 0.88 months for chemotherapy), much worse than the Japanese pivotal study (PFS, 5.2 months; OS, 14.4 months).[3] The authors concluded that the inclusion of primary refractory patients, stricter cORR criteria (8 weeks *vs.* 4 weeks), and a higher incidence of poor baseline prognostic factors may account for the inferior efficacy of mogamulizumab in this trial compared to the Japanese studies. In addition, 40% of the patients on the mogamulizumab arm of this trial had received prior zidovudine/interferon-Alpha (IFNα) therapy, whereas no patient had received it in the Japanese studies, suggesting that mogamulizumab may be less effective after zidovudine/IFNα failure. Key differences in disease biology between western and Japanese ATL may also explain differences in response. For example, the presence of CCR4 gain-of-function mutations that have been associated with better outcomes following mogamulizumab therapy in some studies[22] were not assessed.

Despite the somewhat disappointing results, this is an important study because it gives us the first prospective cohort of homogeneously-treated, non-Japanese ATL

patients, and it defines an important, if still inadequate, benchmark for mogamulizumab in this patient population. The study also exemplifies the futility of standard salvage chemotherapy in R/R ATL, highlighting the importance of ATL patients having access to investigational therapies. Finally, clinically meaningful improvements were evident even after patients had progressed per protocol, underlining shortcomings in the standardized ATL response criteria.

In conclusion, although responses rates were lower than those observed in Japanese studies, performed in a lower risk population with less stringent efficacy end points, the data reported by Phillips *et al.* support the conclusion that mogamulizumab is a better treatment option in the second line for R/R western ATL compared to standard chemotherapy, and it should be considered when clinical trials are not available.

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