Adult T-cell leukaemia/lymphoma in Brazil: A rare disease or rarely diagnosed?

Adult T-cell leukaemia/lymphoma (ATL), caused by human T-cell lymphotropic virus type 1 (HTLV-1) infection has a median survival of 6–8 months. In Japan the incidence of ATL is about 10 times higher than HTLV-1-associated myelopathy (HAM) whilst in other regions the incidence of these consequences is similar. Brazil has a high prevalence of HTLV-1 with HAM cohorts described, but reports of ATL are sparse, leading to the concept that the incidence of ATL is low. Here, the number of ATL cases in Brazil was estimated and compared with cases in the national registry of cancer (RHC) (Ministério da Saúde do Brasil, 2012). Whether the incidence of ATL is genuinely low or ATL is under-diagnosed is discussed.

First, using published estimates of HTLV-1 infected individuals in Brazil: 800,000 (Gessain & Cassar, 2012) – 2,500,000 (Carneiro-Proietti *et al.*, 2002) and a life-time ATL risk of 4% (Iwanaga *et al.*, 2012), 32,000–100,000 can be expected to develop ATL. Based on 75 years life expectancy in Brazil, 427–1,333 cases of ATL/year are expected.

Second, ATL development is linked with mother-to-child transmission. Only 12 % of infections were considered to be acquired through this route but these 96,000–300,000 infant infections carry as much as 20% life-time ATL risk (Nunes *et al.*, 2017). Thus, 19,200–60,000 carriers would develop ATL resulting in 256–800 cases/year.

Third, ATL cases were estimated accounting for differences in HTLV-1 prevalence between Brazil's regions, age and gender, resulting in 856 ATL cases/year (Table I and Table S1).

However, from 1986–2016 only 369 ATL cases were reported in RHC an average of 12 per year (https://irhc.inca.gov.br/RHCNet/visualizaTabNetExterno.action) (Fig 1). Their age ranged from months to >85 years, with 8·4% of cases in

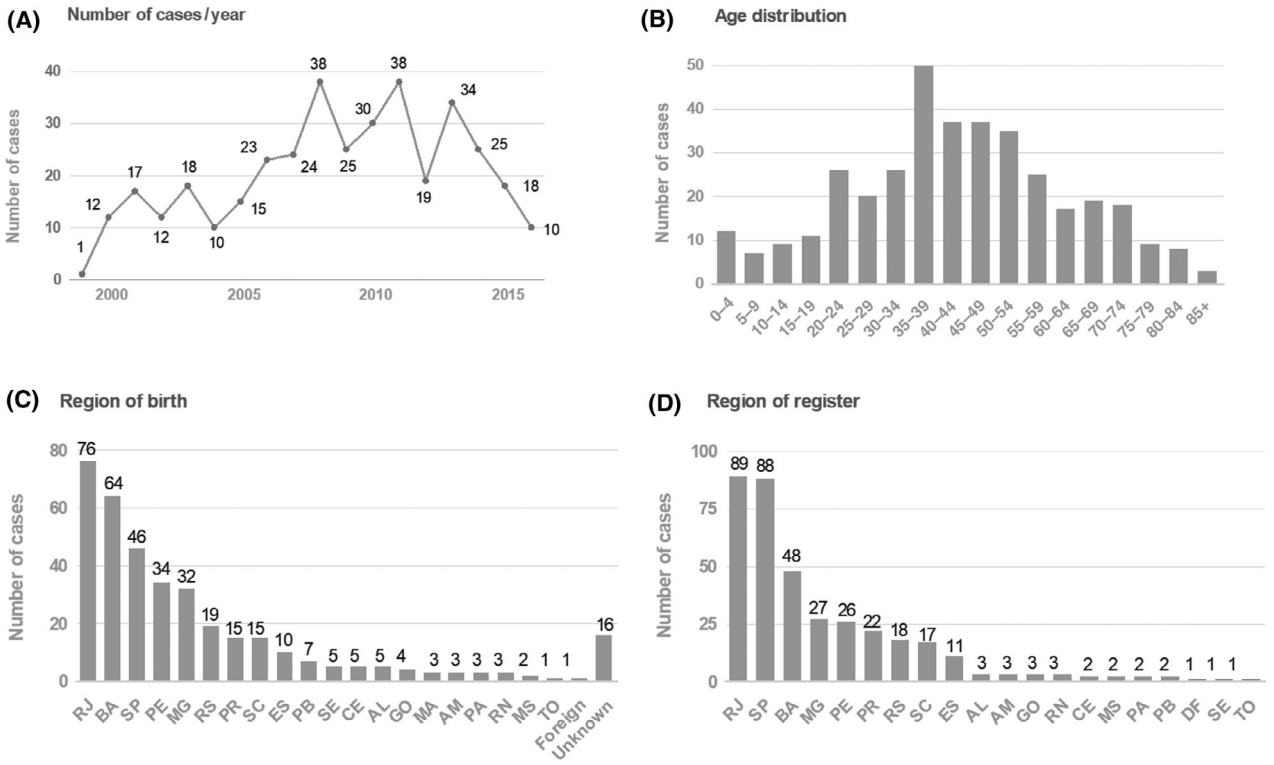

Fig 1. Demographic characteristics of the ATL registered cases in the Hospital Registry of Cancer of Brazil from 1986–2016. (A) Variation of the number of ATL reported cases during the analysed period; (B) Age group at presentation; (C) Brazilian state of patient's birth; (D) Brazilian state of registration. ATL, Adult T-cell leukaemia/lymphoma.

Table I. Expected ATL cases in Brazil and its regions estimated accounting for differences in HTLV-1 prevalence between Brazil's regions, age and gender. The prevalence in women at reproductive age was considered to be the same as pregnant women (Rosadas et al, 2018).

Regions and Gender	Total population	Population by age group (y)			HTLV prevalence (%)			Number of estimated individuals living with HTLV-1 (*n*)				Number of expected ATL cases (*n*)	Expected Incidence (*n*)
		0–14	15–44	>45	0–14	15–44	>45	0–14	15–44	>45	Total	Total	
North													
Total	15,864,454	4,950,677	7,980,600	2,933,177				5,941	21,538	31,650	59,129	**2,365**	31
Male	8,004,915	2,519,951	4,006,780	1,478,184	0·12	0·24	0·96	3,024	9,616	14,191	26,831	1,073	
Females	7,859,539	2,430,726	3,973,820	1,454,993	0·12	0·30	1·20	2,917	11,921	17,460	32,298	1,292	
North-East													
Total	53,081,950	14,104,691	26,230,686	12,746,573				43,725	198,732	388,812	631,268	**25,251**	337
Male	25,909,046	7,174,490	12,860,590	5,873,966	0·31	0·67	2·69	22,241	86,423	157,892	266,556	10,662	
Females	27,172,904	6,930,201	13,370,096	6,872,607	0·31	0·84	3·36	21,484	112,309	230,920	364,712	14,588	
South-East													
Total	80,364,410	17,452,220	39,340,458	23,571,732				45,376	233,992	565,431	844,799	**33,792**	451
Male	39,076,647	8,871,840	19,435,385	10,769,422	0·26	0·53	2·11	23,067	102,619	227,450	353,136	14,125	
Females	41,287,763	8,580,380	19,905,073	12,802,310	0·26	0·66	2·64	22,309	131,373	337,981	491,663	19,667	
South													
Total	27,386,891	5,983,317	13,178,789	8,224,785				2,393	11,868	29,833	44,094	**1,764**	23
Male	13,436,411	3,047,601	6,555,513	3,833,297	0·04	0·08	0·32	1,219	5,244	12,267	18,730	749	
Females	13,950,480	2,935,716	6,623,276	4,391,488	0·04	0·10	0·40	1,174	6,623	17,566	25,364	1,015	
Mid-West													
Total	14,058,094	3,441,390	7,252,400	3,364,304				1,721	8,493	15,799	26,012	**1,040**	14
Male	6,979,971	1,752,662	3,596,714	1,630,595	0·05	0·10	0·42	876	3,741	6,783	11,400	456	
Females	7,078,123	1,688,728	3,655,686	1,733,709	0·05	0·13	0·52	844	4,752	9,015	14,612	584	
BRAZIL													
Total	190,755,799	45,932,295	93,982,933	50,840,571				99,155	474,623	1,031,525	**1,605,302**	**64,212**	856
Male	93,406,990	23,366,544	46,454,982	23,585,464				50,427	207,643	418,583	676,653	27,066	
Females	97,348,809	22,565,751	47,527,951	27,255,107				48,728	266,979	612,942	928,649	37,146	

ATL, Adult T-cell leukaemia/lymphoma; HTLV-1, human T-cell lymphotropic virus type 1 (HTLV-1).

For the older age group, a fourfold higher prevalence was considered while in children was considered to be 40% of the prevalence observed at the 15–45 years age group. Then, as HTLV-1 prevalence is reported to be lower in males, an adjustment was made, multiplying the prevalence in women by 0·8, except for children, in whom we do not expect differences among gender.

The total number of expected ATL cases in each region and in Brazil are presented in bold. The total number of estimated individuals living with HTLV-1 in Brazil is also in bold.

paediatric patients; 51·8% were females. The states of São Paulo, Rio de Janeiro, Bahia, Minas Gerais and Pernambuco had the most registrations. The average time from initial investigation to diagnosis was 0·2 years (maximum 7 years) and to treatment was 0·27 years (maximum 10 years).

In Japan, with a similar number of HTLV-1-infected carriers as Brazil, 800–1000 cases of ATL are diagnosed annually (Iwanaga *et al.*, 2012). If the life-time risk of ATL in Brazil is the same as in Japan or the Caribbean the expected number of cases is ~100-fold higher than those reported but similar to the three estimates presented. Why then are reported cases so few? Since 1993, RHC was implemented in all units with procedures of high complexity in oncology, reaching 268 hospitals in 2012. The data obtained guides public health policies regarding cancer (Ministério da Saúde do Brasil, 2012). Despite that, the number of ATL notified cases is extremely low compared to the expected cases. However, 195 cases were identified over four years (48 cases/year) (Pombo De Oliveira *et al.*, 1999) whilst 287 cases have been published in Brazil (Oliveira *et al.*, 2017). Similarly, only three cases were reported in Pará during 31 years, whereas, a hospital-based study identified four patients with HTLV-1 and Non-Hodgkin lymphoma over 6 years, with 3·2% (4/126) HTLV-1 seroprevalence among patients with leukaemia/lymphoma (Barbosa, 2012). Even in research settings the definitive diagnosis of ATL was hampered by lack of resources. In an HTLV specialised centre in São Paulo, the number of diagnosed ATL cases increased 10-fold after an awareness campaign among clinicians. Most cases were cutaneous with at least one year of disease and with good overall health (personal communication APO). This suggests that acute ATL, the most severe presentation, remains undiagnosed or un-referred to specialised centres. Moreover, the states that reported the most ATL cases were those where the main HTLV research groups are stablished.

In Japan there is a male predominance of ATL; in other regions, e.g. Jamaica, ATL occurs more frequently in females (Iwanaga *et al.*, 2012). In Brazil no gender predominance was observed. The median age at ATL presentation in Brazil is lower than in Japan (44 vs. 68 years) (Iwanaga *et al*, 2012) and despite its name, there are reports of ATL in paediatric patients from different countries (Oliveira *et al.*, 2018). In the RHC 31 cases (8·4%) occurred in children (<18 years old, including infants). These observations are important since long duration of infection, with acquisition of mutations during a life-time period, is considered important to the oncogenesis of ATL. It also highlights the necessity of routine surveillance for ATL in paediatric oncology. In the other hand, the relatively high percentage of paediatric cases also points to under diagnosis amongst adults.

The time between the first consultation to diagnosis and treatment can be up to 7 and 10 years. This reflects the difficulty in the diagnosis even when we consider that those reported cases were seen in reference oncology units. This time can be essential for a better prognosis. The clinical manifestation of ATL is diverse, varying from very aggressive acute forms which are most common to chronic, indolent presentations (Carneiro-Proietti *et al.*, 2002) although these constitute 15% of cases. Acute presentations with hypercalcaemia or opportunistic infections result in patients dying precipitously without a proper diagnosis. The data presented indicate that acute cases are rarely diagnosed in Brazil.

The necessity of more studies regarding ATL in Brazil is clear. Medical training is essential. Many doctors in the country do not know about HTLV-1 despite its high prevalence (Zihlmann *et al.*, 2012). Indeed, when HTLV-1 patients and their relatives listed their main difficulties in Brazil, the lack of knowledge about HTLV-1 among health professionals was the second most important complaint (data not published).

Considering the complexity of clinical manifestation and diagnosis of ATL, the lack of knowledge among health professionals and difficult access to public health care in Brazil, especially in low-income areas, together with the evidence presented here, it is plausible that the reported low incidence of ATL is due to misdiagnosis rather than to low incidence. Further studies are urgently needed to understand the real scenario of this high mortality disease. Furthermore, public health policies aiming to reduce mother-to-child transmission are essential to prevent the majority of ATL cases and should be implemented in the country.

Conflict of Interest

The authors declare no conflict of interest.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Expected ATL cases in Brazil and its regions estimated accounting for differences in HTLV-1 prevalence between Brazil's regions, age and gender.

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Complete remission after the first cycle of induction chemotherapy determines the clinical efficacy of relapse-preventive immunotherapy in acute myeloid leukaemia

Relapse after the completion of induction and consolidation chemotherapy remains a significant cause of mortality in the post-chemotherapy phase of acute myeloid leukaemia (AML). Several studies have questioned whether AML patients who require two or more courses of induction chemotherapy to attain complete remission (CR) are at increased risk of relapse or death. While studies performed in the 1980's and 1990's yielded inconclusive results (Rowe et al., 2010), contemporary studies have identified that needing more than one cycle of induction chemotherapy to achieve CR is a risk factor for relapse and death in younger adult patients (Othus et al., 2019).

Aspects of immunity are relevant to the relapse risk in AML and several immunotherapies aimed at preventing relapse have been developed (Martner et al., 2013; Weinstock et al., 2017; Beyar-Katz & Gill, 2018; Liu et al., 2019). Immunotherapy with histamine dihydrochloride in conjunction with low-dose interleukin-2 (HDC/IL-2) is approved for relapse prevention in AML patients within the European Union (EU). For this study, we analysed the potential impact of previous induction chemotherapy on the clinical efficacy of HDC/IL-2.

Three hundred and twenty patients with AML (18–84 years, median 55), who were not eligible for allogeneic stem cell transplantation, were randomly assigned to receive relapse-preventive immunotherapy with HDC/IL-2 or no treatment (control group) in a phase III trial. HDC/IL-2 was initiated in CR after consolidation chemotherapy (Brune et al., 2006). Patients in the treatment arm were scheduled to receive 10 consecutive three-week cycles of HDC/IL2 with three- (cycles 1–3) or six-week (cycles 4–10) rest periods. In each cycle, these patients received HDC (Noventia Pharma,

