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Multi-step Carcinogenesis Model for Adult T-cell Leukemia

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The age-specific occurrence of adult T-cell leukemia (ATL) was analyzed using 357 cases collected during nationwide surveys carried out between 1982 and 1985 in Japan. A simple Weibull distribution function fitted well as a model. The mode of ATL onset was log-linear in this model and the curves for males and females overlapped completely. The presence of age-dependent accumulation of leukemogenic events within human T-cell leukemia virus type 1-immortalized T cells was suggested prior to the development of ATL, and the approximate number of independent leukemogenic events in ATL is estimated to be five. This stochastic analysis supported a multi-step carcinogenesis as an appropriate model for ATL.

Key words: Adult T cell leukemia — Weibull distribution — Carcinogenesis model

Although seroepidemiological studies[1–4] as well as *in vitro* studies[5, 6] suggest that human T-cell leukemia virus type 1 (HTLV-1) immortalizes human T cells and causes an aggressive type of T-cell leukemia/lymphoma, adult T-cell leukemia (ATL),[7] the virus alone cannot explain the development of ATL because of the presence of a long latency period between HTLV-1 infection and the disease manifestation[7–10] as well as a very low occurrence rate of ATL among carriers of the virus.[9, 11, 12] Recent molecular biological studies have demonstrated that a viral gene product, tax 1 (also called $p40^X$, X-lor, or pX protein), is responsible for activation of cellular genes, such as those for interleukin 2 and its receptor, in some human T-cell lines, thus presenting a possibility that HTLV-1 might be able to immortalize cells via the autocrine circuit consisting of interleukin 2 and its own receptor.[13–15] However, since the leukemic cells in ATL are usually monoclonal, which can not be explained by the autocrine model, additional factors are now under rigorous investigation. This line of thought is also supported by the occurrence of a few ATL cases that are apparently unassociated with HTLV-1,[16, 17] an aspect that will be discussed later. In this study we attempted to clarify the possible natures of these unidentified factors that appear to be essentially involved in ATL leukemogenesis, in addition to HTLV-1 infection, by examining the mode of age-specific occurrence of this disease.

The ages at disease onset for 357 cases of ATL, occurring in 203 male and 154 female patients, collected from thirty-one institutions in Japan during nationwide surveys carried out between 1982 and 1985 were analyzed. These data, supplyed by courtesy of the ATL registry kept by the T- and B-cell Malignancy Study Group in Japan (chief investigator: Dr. M. Shimoyama), were considered to cover approximately one-eighth of all new ATL patients during the observation period.[10, 18] Since recent epidemiological studies have demonstrated that ATL appears to develop mostly in individuals infected from their mothers, probably through breast-feeding,[8, 9, 19, 20] we assumed in the following study that patients developing ATL in later life had acquired HTLV-1 infection during infancy and that, therefore, the age at onset of ATL could be regarded as the incubation period of the disease. We also treated these cross-sectional data as cohort data.

Based on the age-specific distribution of the ages of ATL patients at disease onset, the cumulative incidence of ATL occurrence was analyzed by fitting the data to various distribution models using a computer program (the LIFEREG procedure, SAS Users' Guide: Statistics, Version 5 Edition, Cary, North Carolina: SAS Institute, (1985)). Log-likelihood ratio tests were performed to examine the model-fitting (see ref. 21 for a discussion of the merits as compared with other tests).

The characteristics of the age of disease onset with 357 ATL patients examined in the present study are summarized in Table I. The average ages at ATL onset and their modes for both males and females were the mid-fifties, and were consistent with previous studies.[7, 8, 12] Figure 1 shows the age-specific distribution of disease onset for these ATL patients. ATL development started from the age of 24 years, peaked at 50–54 years and then decreased. A slight decrease in the age rank of 55–59

Abbreviations: ATL, adult T-cell leukemia; HTLV-1, human T-cell leukemia virus type 1.

Table I. Characteristics of the Age at Disease Onset in the ATL Patients Studied[a] and Evaluation of Model-fitting

	Male	Female	Total
Basic statistics			
Numbers of cases	203	154	357
Mean	55.1	55.8	55.4
SD	12.3	12.5	12.4
Median	55	56	55
Mode	63	51	63
Log-likelihood values			
Distribution models:			
Weibull	10.75	8.77	19.35
Gamma	12.95	8.79	20.83
Log normal	8.16	−1.55	6.30

a) Collected between 1982 and 1985 in 31 institutions throughout Japan. For model-fitting, the cumulative incidence curve of ATL cases was analyzed according to each model distribution function with parameters calculated to best fit the original data. Calculations were carried out using the LIFEREG computer program package (SAS Institute, North Carolina, USA). (Comparison and explanation of various distribution models are well described in ref. 21.)

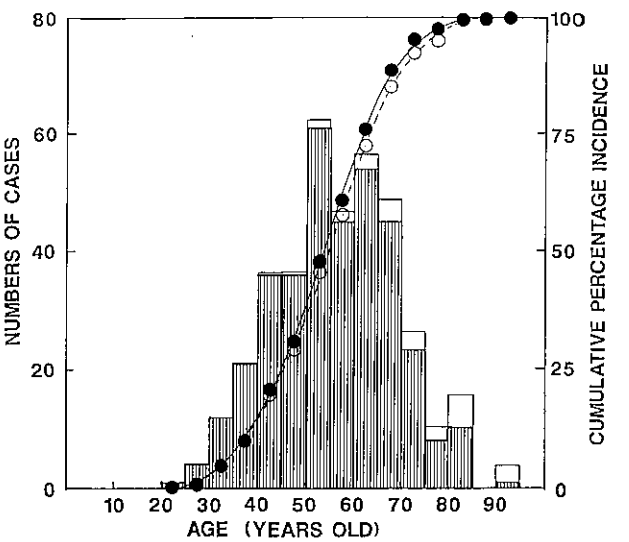

Fig. 1. The distribution of the age at disease onset of ATL patients studied. The original ages were categorized into five-year ranks. The observed number of patients in each rank is represented by a shaded bar (▥). The number of cases in each category was corrected with the accumulated death rate for each age rank according to data from the national population survey in Japan conducted in 1985 (□). The cumulative percentages of ATL occurrence, both observed (●) and corrected (○), are shown by circles and lines.

years was noted in both of two independent surveys (cases diagnosed between 1982 and 1983 and between 1984 and 1985, with no overlapping cases) and was considered to be due to a cohort effect rather than a sampling fluctuation. The observed data were corrected by considering the competing effects of deaths due to other causes according to a life table produced by a national population survey of Japan. Cumulative percentage incidence of these ATL patients is also illustrated in Fig. 1.

The cumulative percentage of ATL occurrence thus obtained was analyzed by fitting the data to various distribution functions using the LIFEREG computer program package. The log-likelihood values calculated for each of the distribution models are summarized in Table I. On the basis of their high log-likelihood values, both the Weibull and the gamma distribution models were accepted.[22-24] However, the former was adopted in this study because of its simplicity as a mathematical model (conceptually, in fact, the former model can be included in the latter). Table II indicates the parameters, estimated in this study, for the density functions to describe the onset age of ATL in male, female and both sexes according to the Weibull model. The parameters, "*a*" and "*b*" in Table II, for the density functions are also known as "shape parameter" and "scale parameter," respectively, and these values are almost constant irrespective of sex. The parameters obtained with the observed and corrected (Fig. 1) data were nearly identical and

Table II. Parameters for the Weibull Distribution Function Estimated in the Present Study

Parameters	Male	Female	Total
a	4.97	5.11	5.03
b ($\times 10^{-8}$)	7.61	8.41	8.00

The Weibull distribution has the density function: $f(t)=a/b\cdot t^{a-1}\cdot\exp(-t^a/b)$, where t is the age (years). The log likelihood values for this model are listed in Table I.

because of the greater log-likelihood values the model obtained with the observed data was used in the following study.

Figure 2 shows a diagrammatic representation of the cumulative incidence of ATL with the data transformed according to the Weibull model (so-called "Weibull plot"). The left-hand panel of Fig. 2 indicates that the distributions for both sexes showed a nearly identical pattern (also confirmed by log-rank and Wilcoxon's rank tests), except for a slightly lower incidence in males younger than 40 years. A comparison of the observed and expected numbers of total ATL cases also showed

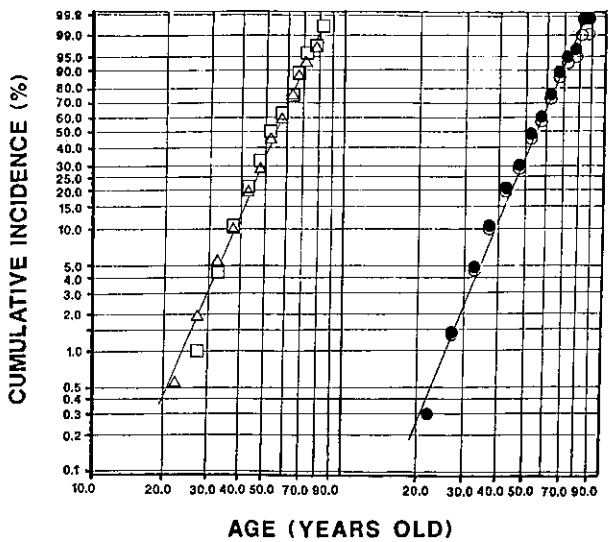

Fig. 2. Weibull plots of the cumulative percentage of ATL occurrence by age. Identical lines were obtained for males (□) and females (△). The Weibull plots obtained with the observed (●) and corrected (○) data also overlapped. The slight upward deviation from the line for the thirties and forties may be attributable to a bias of registration. The calculations were carried out as described in the text. The ordinate indicates $\log\left[\log\frac{1}{1-F(t)}\right]$ and the abscissa, $\log t$.

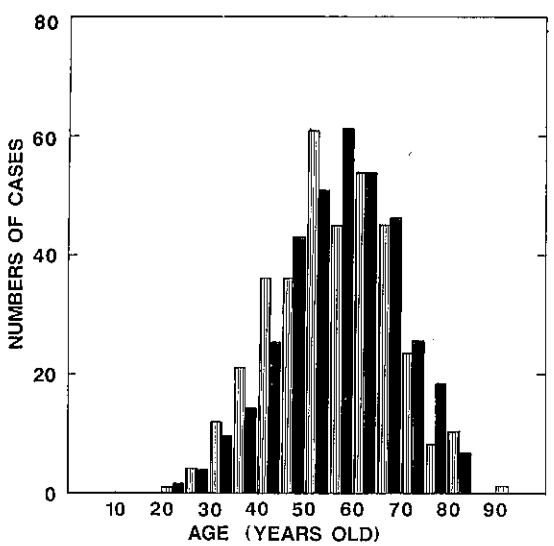

Fig. 3. A comparison between the observed and expected numbers of ATL patients in each age category. ▥, observed; ■, expected. The expected numbers were obtained from the Weibull model as described in the text. Parameter values are listed in Table II.

that the two were identical, as can be seen in the right-hand panel of Fig. 2.

Similarly, Fig. 3 shows a comparison of the observed and expected numbers of ATL patients in each age-rank category under the Weibull distribution model. It is clear that the assumed model agrees with the observed data quite well. Using a simple chi-square test of observed minus expected values, the Weibull model yielded an acceptable fit for the data, as expected from the high log likelihood values. These results support the Weibull model (with the parameters indicated in Table II) as an appropriate model to describe the age-specific occurrence of ATL, thus giving an epidemiological basis for further consideration.

The results of the present study indicate that the age-dependent occurrence of ATL can be simply described by a Weibull model[22-25] of the typical tear-off type and suggest that ATL leukemogenesis might be the result of accumulation of a number of critical events, most likely somatic mutations. Mathematical considerations of multi-step carcinogenesis (see refs. 26 and 27 for reviews) in relation to the Weibull model have been thoroughly discussed by Burch,[24] and based on his assumption the putative number of independent leukemogenic mutations involved in ATL is estimated to be approximately five (represented as parameter "a" in Table II). This estimated number of ATL-prone mutations is similar to the numbers estimated for other malignancies.[22-25] However, such a well matched fit to a single Weibull distribution function has not been reported for other malignancies.

It appears that although HTLV-1 infection plays a primary role in the pathogenesis of ATL as an "initiator" it may be only a prerequisite for accumulation of later events and may not be the direct cause of the disease, unless HTLV-1 is subsequently shown to possess a mutagenic potential in T cells. Similarly, the rarity of HTLV-1-negative ATL[16,17] suggests that ATL could occur without HTLV-1 infection if the T-cell population of a particular differentiation lineage were to be immortalized by another less common mechanism. Furthermore, the life-long rate of ATL occurrence among HTLV-1 carriers has been estimated to be not more than a few percent.[9,10,12] Therefore, it is considered that the rates of ATL-prone somatic mutations are very low and/or that quite a large number of HTLV-1-immortalized cells is required for ATL development within the normal human life span. Currently, we are unable to speculate further on the natures of the target genes for the mutations involved in ATL leukemogenesis. A recent cytogenetic study of 31 ATL cases revealed multiple but no consistent gross chromosomal aberrations,[28] so subtle genetic changes need to be carefully investigated.

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