

Combination therapy and survival time in Adult T cell Leukemia/Lymphoma (ATLL)

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Research article

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Abstract

Background: The urgent need for the treatment of ATLL has highlighted in 18th-International Conference on Human Retrovirology-HTLV-1 (Tokyo, 2017). Therefore, in this study the median survival times (MST) of routine therapies for ATLL were evaluated in context of laboratory tests .

Methods: In a perspective-retrospective cohort study, the efficiencies of therapy regimens, including interferon-alfa and zidovudine (IFN/ZDV), cyclophosphamide, vincristine, doxorubicin, dexamethasone (hyper-CVAD), lenalidomide/ZDV, cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) were evaluated in 67 acute ATLL patients. The demographic, clinical, MST, and routine and molecular laboratory data were then collected and analyzed .

Results: The MST for acute and lymphoma subjects was 5 and 11 months, respectively, including 5 months (95% CI 3.378–6.622) for IFN/ZDV, 5 months (95% CI 2.06–7.94) for CVAD, 3months (95% CI 0.00–9.86) for lenalidomide/ZDV and 11 months (95%CI 8.459–13.54) for CHOP regimen. Importantly, patients who received IFN/ZDV and hyper-CVAD therapy, had a better OS (HR, 0.663; 95%CI, 0.540 to 0.814; P=0.0001), compared with the lenalidomide /ZDV alone. The MST for subjects with hypercalcemia was 5 months, and for patients with normal calcium level was 9 months (p=0.017).

Conclusions: High expressions of BIM and CERB were more frequent in lymphomatous type, and considering these factors, platelet counts and HTLV-1-proviral load (PVL) might be predictive factors for differentiating acute and chronic types. Low MST was observed in acute and lymphomatous ATLL, even in the combinational chemo-therapeutic regimens. Therefore, it seems that ATLL treatment should be personalized according to the virus-host interactions on survival signaling pathways, the platelet count and calcium level.

Introduction

Human T Lymphotropic virus type 1 (HTLV-1) is associated with two life threatening diseases, adult T-cell leukemia (ATLL) and HTLV-1 associated myelopathy/Tropical spastic paraparesis (HAM/TSP). However, only a small proportion (2–5%) of infected subjects develops the diseases, and the majority (95%) remains as healthy carriers, during their entire life[1].The most HTLV-1 infected worldwide regions are Caribbean basin, South America, Central Africa, Southwestern Japan, the Melanesian Islands and the Middle East [2]. Furthermore, at least five provinces of Iran are endemic for HTLV-1 infection, including North Khorasan, Central Khorasan, Golestan, Alborz and East Azerbaijan [3, 4].

Adult T cell leukemia/ lymphoma (ATLL) occurs due to the aggressive T-cell proliferation of the HTLV-1 infected cells. According to different clinical features, the malignancy has been classified into, acute, lymphomatous, chronic, and smoldering subtypes, which are specified by the organ involved, lactate dehydrogenase (LDH) and calcium levels [5].The subtypes of acute and lymphomatous are very progressive, while the most chronic or smoldering ATLL cases are more indolent with survival time of years, even without treatment.

The most prevalent symptoms of ATLL are organomegaly, cutaneous lesions, and hypercalcemia [6]. Moreover, severe hypercalcemia is one of the most challenging complication and the main cause of early death in ATLL infected patients [7]. About 70% of the ATLL patients have high serum calcium levels during the clinical course, particularly during the aggressive stage of ATLL. In these patients, the serum calcium level is often more than 20 mg/mL, and accordingly, most of these patients are susceptible to coma [8]. Therefore, calcium has an important role in pathogenesis and progression toward life threatening state [9–11]. Many different therapeutic regimens were applied in ATLL, in spite of the fact which the authors had promising interpretations, an effective treatment yet to be introduced.

In the present study, the efficiencies of the most used therapy regimens on the survival rate and clinical features, including interferon-alfa and zidovudine (IFN/ZDV), cyclophosphamide, vincristine, doxorubicin, dexamethasone (hyper-CVAD), lenalidomide/ZDV, cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) were evaluated. Moreover, serum calcium levels, hematologic indices and the association of ATL subtypes of newly diagnosed subjects with the gene expression level factors, such as BIM and CREB and viral factors, including Tax and HTLV-1 proviral load (PVL) were assessed for prediction of malignancy.

Materials And Methods

A retrospective study was conducted on the ATLL patients, referred to the oncology-hematology wards in the Ghaem and Emam Rezae Hospitals, Mashhad University of Medical Sciences (MUMS), Mashhad, Iran, between March 2005 and June 2017.

A total of 88 ATLL patients, including 49 males (55.7%) and 39 females (44.3%) were eligible for analysis. The patients were examined by two oncologists. The inclusion criterion was the diagnosis of the acute and lymphomatous type ATLL, based on the Shimoyama classification[12]. All clinical data, as well as the validity of the diagnosis of ATLL were centrally reviewed by two expert hematologists. The Biomedical Ethics Committee approval numbers of the study are MUMS: 911304, 911282 and 930685.

Demographic and clinical data collections

Demographic, clinical subtypes and features (lymphadenopathy, hepato-splenomegaly, respiratory, CNS and gastrointestinal (GI) involvements, skin lesion and B symptom), performance status (PS) by Eastern Cooperative Oncology Group (ECOG), AnnArbor stage and treatment strategies were collected from their clinical charts. Disease was diagnosed based on the presence of more than 1% of abnormal lymphocytes in peripheral blood, according to the definition of diagnosis for acute and lymphoma type ATLL in Shimoyama classification. Overall survival time (OS) was calculated from the time of diagnosis to the last follow-up to death. Data collections were approved by the Biomedical Ethics Committee at MUMS.

Laboratory tests

Laboratory data, including WBC and RBC counts, HCT, abnormal lymphoid cell counts, hemoglobin levels, platelet counts, serum total protein, albumin, LDH, calcium, AST, ALT, ALP, total bilirubin, direct bilirubin, urea, uric acid, creatinine levels were collected from the hospital database. HTLV-1 PVL, Tax, BIM, RAD51 and CREB were obtained from our previous molecular evaluation in which, the survival pathways in transformed ATLL cells were evaluated [13]. Therefore, those variables for shared patients of the present study taken into accounts in the statistical and mathematical analysis.

Statistical Analysis

Baseline characteristics were summarized by frequency distributions and descriptive statistics. The current data on age, median survival time (MST), and OS were compared with 1991 database [12]. OS is defined as time from diagnosis to death, from any cause or to the date of the last follow-up. Patients who are alive at the time of the last sampling were censored at the time of analysis. Survival curves were calculated by the Kaplan–Meier method. Differences in Kaplan–Meier curves were assessed, using the log-rank test. The analyses were performed, using the Statistical Package for Social Sciences' version 16.0 (SPSS, Chicago, IL). In the bivariate analysis, we used the One-way Analysis of Variance (ANOVA) and Pearson's χ^2 tests. Univariate analyses were performed, using the Cox proportional hazard regression model to assess the effect of various factors on OS. Univariate and multivariate Cox regression analyses were applied to evaluate prognosis factors for survival time. The effects of clinical parameters were evaluated as hazard ratios (HRs) and 95% confidence intervals. All tests were interpreted at a predetermined significance level (P value <0.05). In data mining analysis, prognosis was defined based on decision trees, by Rapid miner software V5.3.

Results

Demographic results

The mean age of patients was 56.02 ± 12.72 years (in the range of 2988). According to the Shimoyama classification, from 88 patients (49 men and 39 women) who were diagnosed with ATLL, 67 patients were eligible for analysis. Among 67 selected patients, 33, 31 and 3 patients were diagnosed with acute, lymphoma and chronic type of ATLL, respectively (Figure 1a). The mean age of ATLL patients for acute type, chronic and lymphomatous was 56.22 ± 13.53 , 57.03 ± 14.89 , and 59.33 ± 8.02 years, respectively. No significant differences were found between the mean ages of the patients.

Clinical manifestations

Considering clinical pattern, the most common presenting symptoms were lymphadenopathy (67 cases, 82.7%), hepatosplenomegaly (20 cases, 62.5%), respiratory involvement (28 cases, 42.4%), GI involvement (30 cases, 44.8%), skin lesion (33 cases, 42.9%) and B symptom (76 cases, 98.7%). Five patients (11.1%) had central nervous system (CNS) involvement, detected during their course.

Among 33 patients with skin lesion, erythroderma, patch, plaque, nodulotumoral and purpurictypes' lesions were observed in 20.0%, 15%, 5%, 55% and 5%, respectively, while multipapular lesion was not observed in patients enrolled in this study. The Eastern Cooperative Oncology Group (ECOG) performance status at presentation was 5(13.5%) patients with ECOG PS 0, 1(29.7%) patients with ECOG PS 1, 17(18.9%) patients with ECOG PS 2, 9(24.3%) patients with ECOG PS 3, and 4 (13.5%) patients with ECOG PS 4. Among 31 patients with lymphoma, 4%, 76%, 20% were detected to have Ann Arbor stages I, III, and IV, respectively.

Treatment protocol and survival

Sixty-four patients with aggressive ATLL, lymphomatous and acute types, received treatment. Among those patients with acute ATLL, 25 (28.4%) patients received first-line of antiviral therapy zidovudine and interferon-alfa (IFN/ZDV), 4 (4.5%) patients received cyclophosphamide, vincristine, doxorubicin, and dexamethasone (hyper- CVAD regimen), and 4 (4.5%) patients received the first-line antiviral therapy lenalidomide/ ZDV. All 31 patients with lymphomatous type, received the first-line chemotherapy of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP regimen) (Table.1).

At the time of data analysis, 23 patients (26.1%) were alive and 55 (62.5%) patients were dead. All the patients had been followed up for more than a year, since the onset of the disease.

The OS time was 8 months, and the median survival times (MST) were 5.00 and 11.00 months for acute and lymphoma types, respectively (Figure 1b). As expected, patients with indolent ATLL (chronic or smoldering) had a significant better survival time, compared with the patients with the aggressive ATLL (acute or lymphoma; $P < .001$). MST for patients with hypercalcemia was 5 months and 9 months for patients with normal serum calcium level ($p = 0.017$).

MST was 5 months (95% CI 3.378 6.622), for whom received the first-line antiviral therapy of IFN/ZDV, 5 months (95% CI 2.067.94) for patients who received the first-line chemotherapy hyper-CVAD regimen, and 3 months (95% CI 0.009.86) for whom received the first-line antiviral therapy lenalidomide /ZDV. MST for patients with lymphoma type who received CHOP regimen was 11 months (95% CI 8.459 13.541). Patients with acute ATLL benefited significantly from the first-line antiviral therapy, whereas patients with ATLL lymphoma experienced a better outcome with chemotherapy (Figure 1c).

Laboratory findings

The white blood cell (WBC) counts ranged from 1.1 to $265 \times 10^9/L$, with a median value of $15.615 \times 10^9/L$. The median of calcium level and LDH were 10.10 mg/dL (range, 6.923.7 mg/dL) and 934.500 U/L (range, 180 9109 U/L), respectively.

Predictive findings

The predictive factors of the survival time were considered. In univariate analysis, age, gender, lymphadenopathy, hepatosplenomegaly, GI involvement, B symptom, CNS and skin involvement were not found, as significant factors for survival time. The acute ATLL and lymphomatous subtypes were associated with poorer outcomes, compared with the chronic and smoldering ATLL (HR, 0.331; 95% CI, 0.184 to 0.597; P = 0.000).

Molecular analysis of oncogenes and transcription factors show that if the expression of *BIM* and *CERB* are high, the patient goes to the lymphomatous type. If the *BIM* expression is high and the *CERB* expression is low, a platelet count can differentiate between the acute and chronic types. If the platelet count is above 200,000, it will move toward the chronic type and if the patient's platelet count is low, it will go to the acute type (Figure 2a). If the platelet count is less than 200,000, the high *Tax* expression alone leads to the acute type. If the *Tax* expression is low, the age of the patient differentiates between the acute and lymphomatous types. The age above 57 years old, leads to acute type, while the age under 57 years develops into lymphomatous type of disease. When the patient's platelet count is above the mentioned value, the viral load determines the types, chronic or lymphomatous types of the disease. If the platelet is above 9,000, it will move toward the chronic form and if the patient's viral load is low, it will go to the lymphomatous type (Figure 2b). If the platelet count is less than 60,000, it leads to the lymphomatous type. If the platelet count is between 60,000–200,000, this is the serum calcium level, which discriminates the acute and lymphomatous types. The serum calcium level above 9.300 mg/dL leads to acute type, while serum calcium level under 9.300 mg/dL develops into lymphomatous type of disease. When the patient's platelet count is above 200000, the viral load differentiates the chronic and lymphomatous types of the disease. If the platelet is above 9,000, it will move toward the chronic form and if the patient's viral load is low, it will go to the lymphomatous type (Figure 2c).

If the lymphadenopathy is present, higher WBC count leads to the acute type, while the lower WBC count will be considered as the lymphomatous type of the disease. If the lymphadenopathy is not present, it develops into chronic type of disease (Figure 2d).

Similarly, hypercalcemia, atypical cell count, high serum levels of ALT,AST, direct bilirubin, urea,creatinine, and respiratory involvement, Ann- Arbor stage, PS, type of ATLL and treatment were also associated with lower survival time.

Importantly, patients who received antiviral therapy IFN/ZDV and hyper- CVAD regimen had a better OS (HR, 0.663; 95%CI, 0.540 to 0.814; P = 0.000), as compared with those who received the first-line antiviral therapy lenalidomide /ZDV alone. Moreover, a significant survival advantage was observed for chemotherapy with CHOP regimen (HR, 0.310; 95%CI, 0.172 to 0.559; P = 0.0001).

Discussion

In this study, in the main referral educational hospital for HTLV–1 associated diseases, the clinical features, epidemiological and laboratory data from patients with ATLL were examined, using retrospectively collected data of 88 newly diagnosed patients, from 2005 to 2017 in Khorasan, Iran.

The finding in this study showed that age, gender and marital status had no significant effect on the patients' survival. Consistent with our study, some studies concluded that age, is not a significant factor for survival time [14]. However, the results of some studies suggest that age greater than or equal to 40 years is associated with poorer prognosis of the patients with ATLL [12, 15, 16]. The reason can be explained by the high HTLV-1 prevalence in the elderly people, due to the decrease in the number of HTLV-1 carriers among the young, as a result of the birth-cohort effects, and the continual development of ATLL from this pool of HTLV-1 infected elderly individuals [17].

Our clinical data showed that respiratory involvement, Ann Arbor stage, PS, the ATLL and the treatment regimen were also associated with lower survival rate.

The radiological findings and assessment of ECOG PS involvement, demonstrated the score of more than three organs involvement, the presence of skin lesions and skin lesion type, Ann Arbor stage and inadequate response to chemotherapy were associated with prognosis and survival of patients [17–23]. In the present study, existence and type of skin lesions had no effect on the patients' survival, which was inconsistent with the results of previous studies. The reason for this difference may be the different methodology of the studies.

Here in, results indicated that the median survival rate was 5 months and 11 months for acute and lymphomatous type, respectively. Among the treatments prescribed for the acute type of the disease, the median survival rate for interferon alpha (IFN- α)/zidovudine (ZDV) and the hyper-CVAD regimens was 5 months, while using lenalidomide/ZDV regimen had a lower survival time. However, in AML in a salvage therapy after stem-cell treatment, had very promising outcome [24].

Several studies have been conducted to predict prognosis and to determine the appropriate treatment strategy for different types of ATLL. The results of some studies have suggested the use of ZDV and IFN- α as the first-line and the gold standard for the treatment of acute type [14, 15, 25–27]. Our previous study, using IFN- α /ZDV/ arsenic had a good survival rate in acute ATL [27] and the molecular findings demonstrated an immune response shift from a Treg/Th2 before treatment, toward a Th1 cell-mediated phenotype, after the treatment. Moreover, this triple regimen may have promising results in restoring an immuno-competent Th1 microenvironment, which enhances the elimination of acute ATL and the prevention of opportunistic infection [28].

Several studies have focused on the necessity of the chemotherapy in acute, lymphomatous and unfavorable chronic type, and the use of VCAP-AMP-VECP regimens [15, 17, 29, 30], CHOP [14, 15, 17, 30, 31], OPECMPEC or DOEP [32] regimens have been associated with improved overall response to the treatment and MST.

Although, previous studies showed that using allo-HSCT in controlled amounts of GVHD can improve the patients' survival with an acute form of ATLL [14, 17, 29, 30, 32–39], but our study revealed that none of the patients underwent allo-HSCT.

Several reports followed up the effective therapies for ATLL, including de-fucosylated humanized anti-CC chemokine receptor 4 monoclonal antibodies, IL-2-fused with diphtheria toxin, histone deacetylase inhibitors, purine nucleoside phosphorylase inhibitors, protease inhibitors and lenalidomide [29]. The use of monoclonal antibodies against CC receptor type 4 chemokine (mogamulizumab) has been associated with promising results in the treatment of the ATLL patients, especially in the chemotherapy-resistant ATLL patients. The use of this new drug may improve the condition before allogeneic HSCT and can result in longer patients' survival [14, 29, 30, 32, 40].

The laboratory data indicated that serum calcium, LDH, ALT, AST, direct bilirubin, urea, and creatinine levels, and atypical cell count were related to the patients' survival.

According to the results of multivariate analysis, serum LDH levels [12, 15, 37, 41–47] and hypercalcemia [12, 15, 37, 41–46] have been evaluated as a major prognostic criterion. Additional factors associated with poor prognosis, include WBC count [43, 44, 46], thrombocytopenia [18], eosinophilia [48], atypical ATL cell count in peripheral blood [39, 44, 49], total protein levels [12, 37, 45], low serum albumin levels [16, 50], high blood urea [50], high levels of creatinine [51], and HTLV-1 PVL [17, 37]. The reason for the possible difference between the results of the previous studies and our study, might be the different methodology. Due to the poor prognosis of acute and lymphomatous types of ATLL, lack of proper data on the survival time of these patients, more prospective cohort studies should be conducted to compare the potency and efficacy of the new and routine therapy regimens. Furthermore, considering the nature of the study, similar prospective epigenetics studies are recommended to determine appropriate prognostic markers in a personal medical manner. Such study may help finding the main signaling pathways for targeting in immunotherapy. Therefore, taken into account our previous and the present study, we can suggest that treatment should be personalized for each patient, according to the epigenetics condition such as the oncogene expressions and cell survival signaling pathways in malignant cells. Our data show that platelet count, serum calcium levels and WBC counts can distinguish between acute and lymphomatous types of disease. In addition, platelet count and viral load are helpful to differentiate between lymphomatous and chronic types.

As it can be concluded, poor response or low survival rate was seen in the acute and the lymphomatous form of ATLL, and in the combinational chemotherapeutic regimens, such as CHOP and CVAD, which are the first line choice for ATLL treatment. Other studies had reported such results for aggressive type [17]. Another possible cancer treatment is allogeneic hematopoietic stem forms of ATLL, for which stem cell bone marrow transplantation was performed and like other therapy, no satisfying results have been found. Therefore, new strategies were introduced to cure the ATLL with the immunotherapeutic agents, such as INF in combination with antiretroviral drug AZT [52]. However, it was not efficient in the treatment of lymphoma and acute types, as hypothesized in first studies. Furthermore, findings indicate the side effects of INF/AZT treatment were another dilemma for usage. Even in one of our previous phase II clinical trials, using combination of IFN α /AZT/Arsenic had promising results, but has not being successful as an effective treatment and has not been utilized by other groups [27].

Our recent system biology study showed that three signaling pathways can be targeted in ATLL;BCRA1, AKT/mTOR and VEGFR [53], targeting *BRCA1* or *BRCA2* suppression, using PARP inhibitors (PARPi), shows 70 percent response in a wide range of cancers, such as ovarian, breast, colon and leukemia, leading to the accumulation of DNA damage and resulting in cancer cell death [54]. However, the monitoring of PARPi efficiency in cancer therapy has shown that other pathways in DNA repair, such as RAD51, can produce resistance to PARPi in cancer therapy [55]. We have previously shown that RAD51 was strongly overexpressed in ATLL patients [13]. Therefore, it seems that the usage of PARPi medication, like what it was used for leukemia, along with a RAD51 inhibitor might be effective for ATLL treatment. Since still no RAD51 inhibitor is available, it seems that anti- PARP alone does not produce effective treatment. The apoptosis induced by cAMP correlated tightly with BIM protein expression. It was abrogated by BIM down regulation that may be achieved by the CREB antagonists [56]. Interestingly in this study, the predictive findings of molecular analysis for oncogenes and transcription factors show that if the expression of *BIM* and *CERB* are increased, the patient goes to the lymphomatous type instead of acute type.

With respect to outcome of the 18th International Conference on Human Retrovirology-HTLV-1 (Tokyo, 2017) the need for additional clinical trials to develop novel standard therapies were highlighted, the present study was conducted [57]. The findings showed a very low MST in the most used current combination therapies for ATLL patients. Taken together with those suggestions and the results of this study, the urgent need for introducing effective treatment must be brought to the attention of the researchers. Furthermore, using data mining, low-cost and molecular prognostic indicators were presented in which the low cost prognostic one could be the evaluation of serum calcium levels, platelet count, the WBC count and viral load. In the molecular level, prognostic indicators were HTLV-1 PVL, HTLV-1 Tax and BIM, in the context of calcium and PLT.

Declarations

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Authors' contributions: S. A. Rahim Rezaee and Hossein Rahim designed the study.

Zahra Rezaei Borojerdi, Hiva Sharebiani, Faezeh Sabet and Sanaz Ahmadi Ghezeldasht performed the experiments. Zahra Mozaheb, Alireza Bary and Seyyedeh Tahereh Mohades analyzed the data. Sanaz Ahmadi Ghezeldasht, Hanieh Tarokhian, Sajad Ataei Azimi, Seyyedeh Tahereh Mohades, Abolghasem Allahyari and Abbas Shirdel wrote the manuscript. All authors approved the final version of the manuscript.

Ethics approval and consent to participate

This study was reviewed, approved and supervised by Mashhad University of Medical Sciences Biomedical Ethics Committee (IR.MUMS.REC.970962). The written informed consents were obtained from all the patients and control subjects.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and/or analyzed during the current study are included in this paper and available from the corresponding author (SAR. Rezaee).

Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1. Treatment strategy for all patients enrolled in this study.

subtype	treatment	frequency	
		number(n)	percent
acute	Arsenic. INF. zidovudin	25	28.4
	hyper CVAD	4	4.5
	lenalidomide.zidovudin	4	4.5
lymphoma	CHOP	30	34.1
chronic	Watchful Waiting	1	1.1
	arsenic	2	2.3

Figures

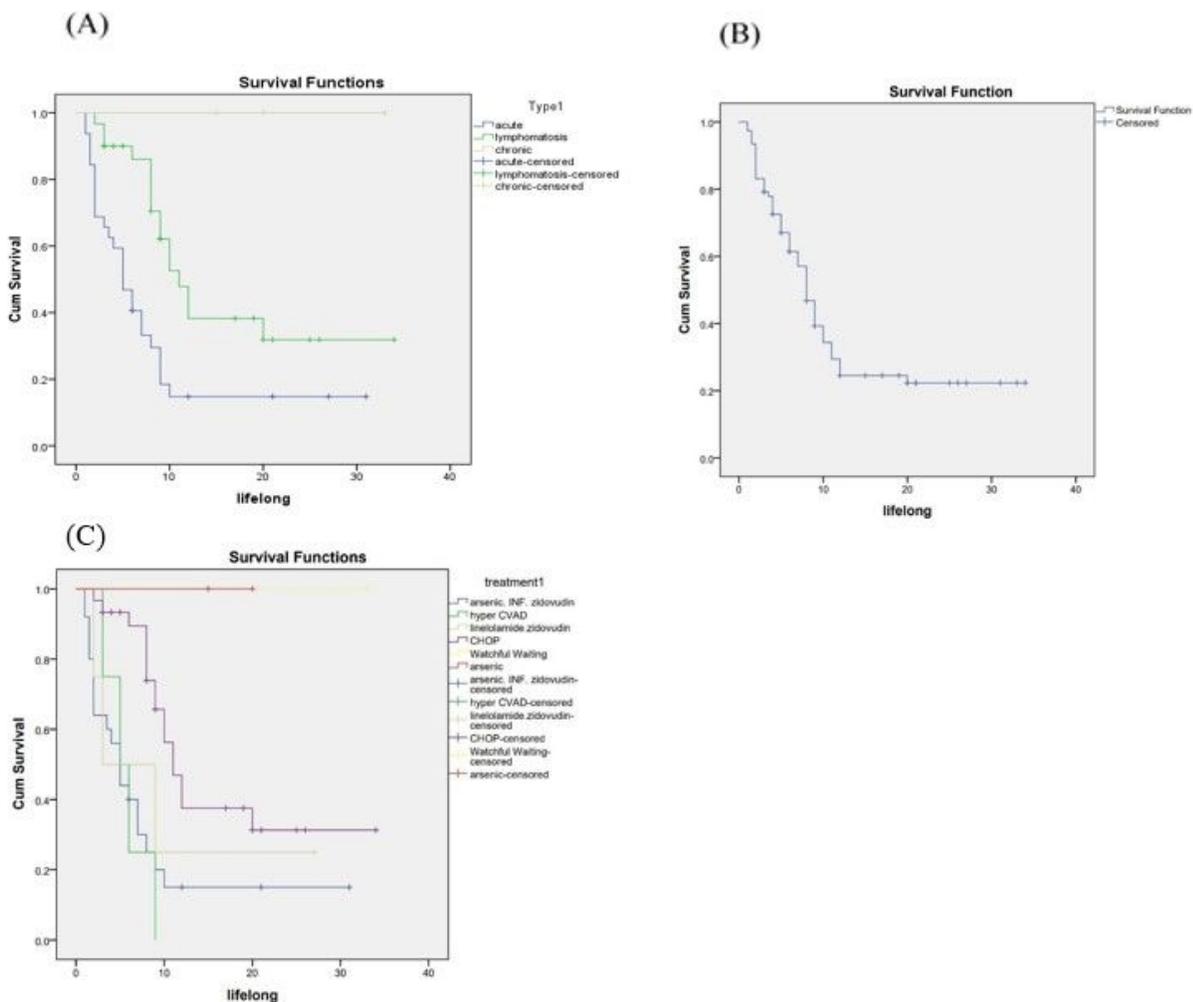


Figure 1

The data on age, median survival time (MST), and OS were compared with 1991 database12. OS is defined as time from diagnosis to death, from any cause or to the date of the last follow-up. Patients who are alive at the time of the last sampling were censored at the time of analysis. Survival curves were calculated by the Kaplan–Meier method and the statistical differences with log-rank test. A: Kaplan-Meier curve for ATL types of the patients. B. Overall survival time of the patients. C. Kaplan-Meier curve for treatment of the patients.

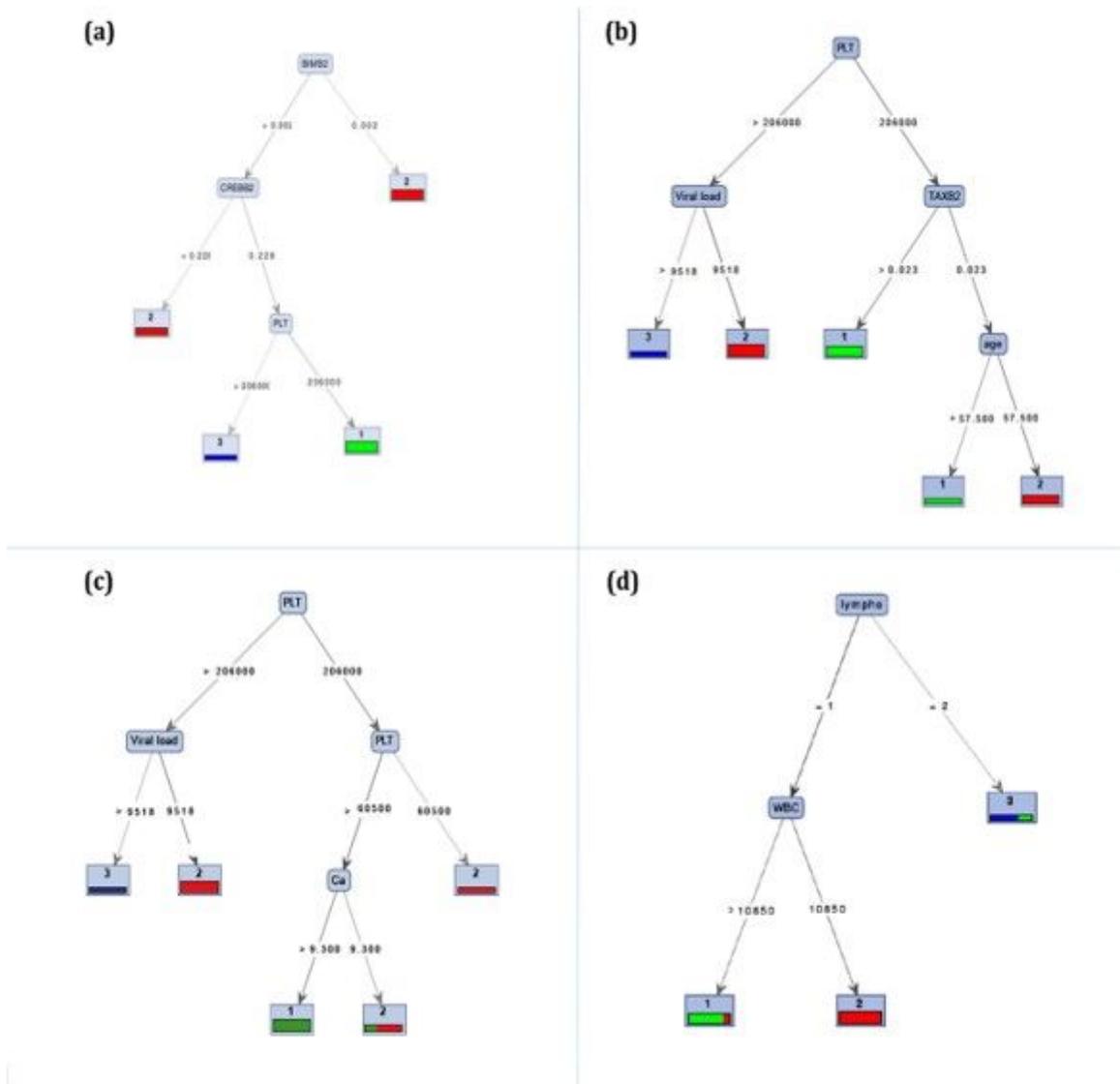


Figure 2

Prognosis for molecular and routine laboratory examination was defined based on decision trees by the Data mining analysis, Rapid miner software V5.3. a) Based on BIM as the main prognostic factor and

CREB. b) Based on Platelet count as the main factor and HTLV-1 proviral Load. c) Based on Platelet count as the main factor and HTLV-proviral load and Ca. d) based on the form of the symptoms as the main factor and WBC.