

Table 1. Jehovah's Witnesses with acute leukemia.

N°Age/Sex (years)	FAB	Therapy	BMT/ABMT	Result	Status	Follow-up
1 11/M	ALL-L2T	AIEOP	BMT	PR	Dead	8 months
2 23/M	AML-M4	FLAI-5	ABMT	CR	Dead	9 months
3 17/F	AML-M3	AIDA	None	CR	CR	14 months
4 30/M	ALL-L3	Magrath	ABMT	CR	CR	12 months
5 44/F	ALL-L2	GIMEMA	None	NE	Dead	6 days

CR=complete remission, PR=partial remission, NE: not eval

nine months after transplantation.

Case #3 was a 17-year old girl who presented in June 1999 with AML-M3. We modified the schedule of AIDA by reducing, at the beginning, the number of doses of idarubicin which were rescued later. She obtained hematologic and molecular remission without platelet support and now, following consolidation, is under maintenance therapy.

Case #4 was 30-year old man diagnosed as having ALL-L3 in September 1999. He received Magrath's protocol for Burkitt's type lymphoma. He obtained remission eighteen days following the start of therapy with a drop of hemoglobin to 5.9 g/dL. With erythropoietin administration his hemoglobin level rapidly recovered and he completed all four phases of treatment and received an autologous PBSC as consolidating treatment. At no time did he have any transfusions of blood products.

Case #5 was a 44-year old woman with ALL-L2; because of a delay of one month her hemoglobin level was 5.4 g/dL at the time therapy was started: she died because of anemia 6 days later.

The treatment of acute leukemia is strongly linked to the possibility of transfusing patients; however we demonstrated that chemotherapy in conventional protocols and allogeneic or autologous BMT could be applied without blood support. Few experiences on successful treatment of acute leukemia without transfusions in Jehovah's Witnesses have been reported.^{3,4} A relevant point is that therapy with conventional protocols should be started as soon as possible because one week of treatment and two weeks of marrow aplasia following treatment in order to get remission may be an acceptably short period of time to have a level of Hb still compatible with life before recovery begins. Some patients not transfused during the course of therapy for acute leukemia have the possibility of reaching complete remission with few adjustments of protocols; we are convinced that the possibility of inducing remission without transfusions is easier in patients with ALL than

AML because the myelopoiesis emerges earlier after the beginning of therapy. However a shorter induction therapy than that actually proposed in schemes for AML could be the choice. We conclude that the medical challenge is always, despite the difficulties, to give a chance of cure to patients.

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Telomerase: obviously activated in the accelerated phase of chronic myeloid leukemia

We report that the telomerase activity of bone marrow samples from accelerated phase and blast crisis chronic myeloid leukemia (CML) was higher than that in chronic phase CML and control samples. This difference might be due to the number of immature cells, but some inherent changes might also exist during the transformation of CML.

Sir,

Telomerase is a ribonucleoprotein polymerase that synthesizes telomeric repeats on the 3' ends of eukaryotic linear chromosomes to maintain telomeres.¹ Numerous reports have presented that telomerase activity was expressed in most human tumor cells, but not in normal cells, except germ line cells, hematopoietic stem cells and activated peripheral blood lymphocytes,²⁻⁵ which suggested that the activation of telom-

Table 1. Telomerase activity of bone marrow samples from CML patients and controls with non-malignant diseases.

Source	Cases	Telomerase activity†	
		average	range
HEK293‡		100.00±0.00	
Control BM	10	11.81±0.67	9.54 -15.51
CML			
chronic phase	31	26.48±15.48*	9.98-71.46
accelerated phase	13	78.85±26.20#	48.97-123.12
blast crisis	21	93.39±26.47#	60.62-136.26

†The telomerase activity of samples was reported as the relative value, which was calculated as follows:

$$\text{Sample relative value} = \frac{\text{Sample absorbency value}}{\text{Positive control absorbency value}} \times 100\%$$

‡. HEK293 cell line, human embryonic kidney cell line 293, was provided by the manufacturer, and used as positive control. *. Compared with control bone marrow, $p < 0.05$. #. Compared with chronic phase, $p < 0.001$

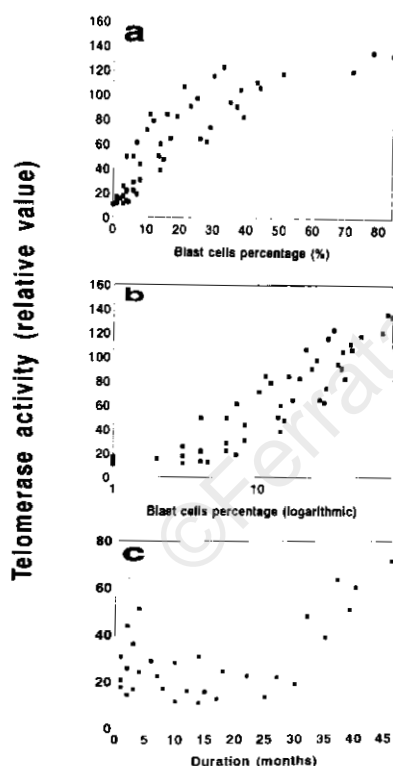


Figure 1. The telomerase activity of CML corresponding to the blast cell percentage (a), the logarithm of blast cell percentage (b) and the duration from the time of diagnosis to the time when the bone marrow sample was obtained (c). The R-value of figure (b) is 0.8972. Through statistical treatment, we obtained the linear equation of figure (b): $y = 9.66 + 68.26x$, and the curve equation of figure (a): $y = 9.66 + 68.26 \lg x$. In figure (c) there is no significant difference before 32 months, though a slight lowering tendency was noticed. After 32 months telomerase activity was remarkably increased ($p < 0.05$).

erase might correlate with cell immortality.^{3,6}

To explore the role of telomerase activation in the progression of chronic myeloid leukemia (CML), 65 bone marrow samples obtained from 62 Ph+ CML patients and 10 control bone marrow samples obtained from the ribs collected during surgery in patients with heart diseases patients were investigated by use of the Telomerase PCR-ELISA kit (Roche Co.). All CML and control samples showed detectable telomerase activity, which ranged from 9.54 to 136.26. The telomerase activity in the chronic phase was higher than that in control samples. In the accelerated phase and blast crisis, significant increase of telomerase activity was detected compared to that in the chronic phase. However, no statistical difference was noted between the accelerated phase and blast crisis. Recently, Ohyashiki and Boulwood reported that telomere length was shorter and telomerase activity higher in the blast phase than in the chronic phase.^{7,8} Our results showed that telomerase activity increased obviously in the accelerated phase, suggesting that the activation of telomerase might be associated with the transformation of CML.

The duration from the time of diagnosis to the time when the bone marrow sample was obtained was calculated for every chronic phase patient. Telomerase activity corresponding to the duration is shown in Figure 1. The difference of telomerase activity between two groups (before and after 32 months) is significant ($p < 0.05$). Remarkably, an increase in the percentage of blast cells was noted in one patient in the latter group. After 3 months his telomerase activity had increased from 71.46 to 91.41, and he had already progressed into clinical accelerated phase disease. It is implicit that the measurement of telomerase activity may be a useful marker for predicting the progression of CML.

Statistical analysis showed a linear correlation between telomerase activity and the logarithm of the bone marrow blast cell percentage. The R-value is 0.8972, and the curve equation is $y = 9.66 + 68.26 \log x$. Ohyashiki once reported that no significant difference in peripheral blood or bone marrow blast cell percentage at the blast phase was evident whether the cells had high telomerase activity or not.⁷ Moreover, Iwama reported that percentages of bone marrow blast cells did not differ significantly between chronic phase CML with normal and shortened telomere length.⁹ Nevertheless, our results suggest that the difference in telomerase activity during chronic and accelerated phase might be due, to some extent, to the number of immature cells. From the curve equation we note that the increase of telomerase activity was obviously faster than the

change of blast cell percentage, which suggests that some inherent changes might also exist during the transformation of CML.

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Fludarabine therapy in chronic lymphocytic leukemia-associated severe nephrotic syndrome

We present a rare case of leukemia-associated membranous nephropathy presenting as severe nephrotic syndrome. Fludarabine treatment was successful in inducing an effective remission from the chronic lymphocytic leukemia and complete resolution of proteinuria.

Sir,

While the majority of patients with chronic lymphocytic leukemia (CLL)-associated nephrotic syndrome (NS) have been found to have membranoproliferative glomerulonephritis, about 20% have either membranous glomerulonephritis or minimal change disease.¹ Available evidence suggests that NS associated with CLL is related to immune-complex disease. Remission induction of glomerular disease with successful treatment of the leukemia provides further indirect evidence that testifies to the paraneoplastic nature of the glomerular involvement.² A 56-year old previously healthy female was seen for evaluation of leukocytosis. Physical examination revealed cervical lymphadenopathy. A hemogram showed a white blood cell (WBC) count of 41.4×10^9 cells/L with an absolute lymphocyte count (ALC) of 32.7×10^9 /L, hemoglobin of 13.8 g/dL, and platelet count of 346×10^9 /L. A peripheral blood smear showed mature lymphocytosis and smudge cells. Flow cytometry of peripheral blood lymphocytes demonstrated a clonal B-cell process consistent with CLL. She was observed with frequent monitoring of her blood counts. Two years later, she presented with a rapid tenkilogram weight gain, peripheral edema and hypertension. Serum albumin was 2.6 g/dL, creatinine 3.8 mg/dL, and cholesterol 406 mg/dL. A 24-hour urine collection contained 19.2 g of proteins. Urine electrophoresis failed to identify monoclonal protein excretion. Percutaneous renal biopsy revealed membranous glomerulopathy. Her WBC count was 73.3×10^9 /L (ALC: 61.6×10^9 /L), and hemoglobin was 9.9 g/dL. The patient was treated with three courses of intravenous fludarabine 25 mg/m² daily for 5 days repeated every 4 weeks. The patient showed a remarkable response to therapy. One month after the third dose, she had complete resolution of edema, WBC count decreased to 3.7×10^9 /L (ALC: 1.11×10^9 /L), and urinary protein excretion dropped to 3.4 g/day (Figure 1). Serum creatinine had decreased to 2.0 mg/dL, serum cholesterol decreased to 253 mg/dL and serum albumin increased to 3.8 g/dL. One year after therapy, the urinary protein excretion is 102 mg/day and ALC is stable around 2.3×10^9 /L. About 35% of patients refractory to previous cytostatic treatment and about 75% of untreated patients obtain complete remissions with fludarabine.³ Fludarabine, a purine analog, appears to be an effective initial induction therapy with a reasonable safety profile for patients with CLL.⁴ In resting lymphocytes the accumulated triphosphate fludarabine derivatives result in defects in the repair of DNA, DNA strand breaks, activation of endogenous nucleases, depletion of nicotinamide adenine dinucleotide