Moreover, aspirin crosses the placenta into the fetus and combinations of UFH or LMWH with aspirin may also increase bleeding tendency in the mother. Thus, the routine use of aspirin in thrombophilic women cannot be advocated.

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To the editor:

Natural course of HTLV-1 carriers with monoclonal proliferation of T lymphocytes ("pre-ATL") in a 20-year follow-up study

Previously we reported that asymptomatic human T-cell lymphotropic virus type 1 (HTLV-1) carriers with a monoclonal proliferation of HTLV-1-infected T cells ("pre–adult T-cell leukemia [ATL]") could account for about 1.7% among a total of HTLV-1 carriers in Japan, and that the pre-ATL subjects had a high potential to develop overt adult T-cell leukemia/lymphoma (ATL/L) and a poor prognosis.1-3 Here we report a further analysis of 50 pre-ATL subjects1 who were enrolled and followed during October 1976 to December 2003 to evaluate their outcomes in Nagasaki prefecture, an endemic area of ATL/L in Japan. Detection assays of the integration band of the HTLV-1 provirus genome were described previously.4 There were 3 end points evaluated: the development of overt ATL/L, death from ATL/L, and overall survival. The diagnostic criteria for overt ATL/L were based on the Lymphoma Study Group (LSG) classification.5 Time-to-event probability was estimated by the Kaplan-Meier methods. Entry age, sex, white blood cell (WBC) count, relative lymphocyte (rLy) counts, and relative abnormal lymphocyte (rAbLy) count were considered as potential prognostic factors. Effects of these factors were evaluated by the Cox proportional hazard regression.

Among 50 subjects, 21 (42%) progressed to overt ATL/L (the incidence rate: 48.0 per 1000 person-years), and 31 (62%) died, of whom 21 died from ATL/L itself. The remaining 10 subjects died of opportunistic infections such as Carinii pneumonia or other malignancies (skin carcinoma, lung cancer, etc). In the univariate analyses, subjects with a WBC count more than 9000/µL showed a higher risk for the development of overt ATL/L compared with those with a WBC count less than 9000/µL (hazard ratio [HR], 3.93; 95% confidence interval [CI], 1.50-10.0). The effect did not change even in an adjusted analysis for other factors. A higher rAbLy count (more than 50%) was also associated with the development of overt ATL/L (HR, 3.04; 95% CI, 1.16-7.95). A higher rAbLy count and older entry age (older than 56 years) were marginally associated with overall survival (data not shown). The comparison of the cumulative probability between the 2 groups of WBC counts showed a significant difference in the development of overt ATL/L (85.7% vs 33.0%) and in death from ATL/L (87.0% vs 72.3%), but no difference in the overall survival rate (Figure 1).

Several Japanese cross-sectional surveys reported a crude annual incidence of ATL/L ranging from 50 to 150 per 100 000 HTLV-1 carriers.6,7 Although our results may overestimate the risk because we did not take a competing risk of death into consideration, the results indicate that the pre-ATL subjects have a high potential to develop overt ATL/L among HTLV-1 carriers. Notably, most of the subjects with a WBC count above 9000/µL developed overt ATL/L, suggesting that those should be considered as the “early stage of ATL/L.” On the other hand, about two thirds of the subjects with a WBC count below 9000/µL never developed overt ATL/L, suggesting that those would be literally in the “premalignant state.” The screening of the pre-ATL subjects from the

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Figure 1. Kaplan-Meier analyses for 3 end points of interest by 2 categories of white blood cell count. Among 20 subjects with a white blood cell count above 9000/µL, 15 developed overt ATL/L, 15 died from ATL/L, and 1 died from other disease. Among 30 subjects with a white blood cell count below 9000/µL, 6 developed overt ATL/L, 6 died from ATL/L, and 9 died from other causes. All comparisons were performed using the log-rank test. (A) The cumulative probability of the development into overt ATL/L was 85.7% in the group with a white blood cell count above 9000/µL versus 33.0% in the group with a white blood cell count below 9000/µL (P = .0028). (B) The cumulative probability of death from ATL/L was 87% in the group with a white blood cell count above 9000/µL versus 72.3% in the group with a white blood cell count below 9000/µL (P = .0048). (C) The overall survival was 12.0% in the group with a white blood cell count above 9000/µL versus 18.0% in the group with a white blood cell count below 9000/µL (P = .20).
HTLV-1 carriers and paying attention to WBC count are clinically important for predicting the outcome of HTLV-1 carriers.

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To the editor:

Imatinib mesylate in the treatment of c-kit–positive acute myeloid leukemia: is this the real target?

Kindler et al reported that 5 of 21 acute myeloid leukemia (AML) patients responded to treatment with imatinib mesylate, which is a c-kit inhibitor. From February 2003 to November 2003, we treated with imatinib 36 c-kit–positive AML patients who were not amenable to conventional chemotherapy. Of the patients, 51% were refractory/refractory and 49% were previously untreated. The median age was 66 years (range, 26-79 years). The median white blood cell count was 4.8 × 10^9/L (range, 0.7-88 × 10^9/L). In addition to a diagnostic panel of monoclonal antibodies, the leukemic blast cells of all the patients were assessed by flow cytometry for c-kit and platelet-derived growth factor receptor β (PDGF-Rβ; phycoerythrin-conjugated anti-CD117 and anti-CD140 monoclonal antibodies; Becton Dickinson, Mountain View, CA) and by reverse-transcription–polymerase chain reaction (RT-PCR) for bcr/abl rearrangement. All of the patients had c-kit–positive blasts (median, 55%; range, 16%-96%), with a high mean fluorescence index (median, 30; range, 17-100; evaluated on 17 cases). Only one patient overexpressed PDGF-Rβ on blast cells (46%). No patient was positive for bcr/abl rearrangements. The median administered dose was 600 mg/d (range, 200-700 mg/d), for a median of 31 days (range, 2-311+ days). Nonhematologic toxicity was mild and not different from the one found in chronic myeloid leukemia imatinib trials. While on therapy with imatinib, 6 patients died (2 with multiorgan failure, 2 of disease progression, and 2 of cerebral stroke). During the follow-up, 15 patients died mainly due to disease progression. No patient achieved a complete or a partial remission. In 2 patients, the disease remained stable as defined by no peripheral blood or bone marrow modification. They are now continuing imatinib after 270 and 311 days. The patient with PDGF-Rβ overexpression had a platelet increase that lasted for one year with transfusion independence. In the meanwhile, blast cells became PDGF-Rβ negative.

Our purpose was to evaluate the in vivo effect of imatinib on c-kit–positive leukemic blasts. In accordance with the findings of Cortes et al and Heinrich et al, we did not find a significant in vivo activity of imatinib, even though the drug is a proven c-kit in vitro inhibitor. On the other hand, Kindler et al obtained 5 hematologic responses, complete and partial. We agree with the hypothesis that multiple gene aberrations sustain leukemic proliferation and that c-kit itself may be useful but not necessary for leukemic cell survival and proliferation. One positive effect was observed in the PDGF-Rβ-positive patient. In vivo PDGF-Rβ-positive blast cells may be more sensitive to the drug, as previously reported. This is in line with the reports on the efficacy of imatinib in the hypereosinophilic syndrome, where PDGF-Rβ expression is secondary to the rearrangement of the PDGF-R gene with the FIP1L1 gene. Since the percentage of AML patients with PDGF-Rβ rearrangement or overexpression is unknown, it could be interesting to screen all patients at diagnosis, for a prospective and proper use of imatinib in the patients who are positive or rearranged.

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