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Nation-wide randomized comparative study of doxorubicin, vincristine and prednisolone combination therapy with and without L-asparaginase for adult acute lymphoblastic leukemia

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Abstract

A randomized clinical trial of combination chemotherapy for adult acute lymphoblastic leukemia (ALL) with doxorubicin, vincristine and prednisolone with and without *L*-asparaginase (AdVP vs L-AdVP) was conducted, involving 58 institutions throughout Japan. After reaching complete remission (CR), patients were treated with the same regimen for more than 2 years. Among 166 evaluable cases of the 198 cases enrolled, CR rates were 63.1% (53/84) with AdVP and 64.6% (53/82) with L-AdVP (P = 0.837). Median survival times and 7-year survival rates were 12.7 months and 21.2% with AdVP, and 16.0 months and 22.3% with L-AdVP (P = 0.955 by generalized Wilcoxon test [GW], P = 0.952 by log-rank test [LR]). Median disease-free survival times and 7-year survival rates were 13.5 months and 23.8% with AdVP and 17.0 months and 30.6% with L-AdVP, showing some increments for L-AdVP but no statistical significance (P = 0.141 by GW, P = 0.300 by LR). Among the cases of extramurally confirmed FAB subtypes, CR rates were 75.9% (63/83) for the L1 subtype and 51.3% (39/76) for the L2 subtype (P = 0.001). As to adverse effects, pancreatitis was complicated more frequently in L-AdVP than in AdVP (P = 0.039). Other side effects such as hyperbilirubinemia, diabetes mellitus, diarrhea and hypofibrinogenemia were observed more frequently with L-AdVP, but with no statistical significance. Thus, addition of a single course of L-asparaginase in the induction phase of combination chemotherapy with doxorubicin, vincristine and prednisolone did not significantly enhance the effect of antileukemic treatment of adult ALL.

Introduction

Therapy in childhood acute lymphoblastic leukemia (ALL) has improved greatly, with a complete remission (CR) rate of over 90% and a 5-year disease-free survival (DFS) rate of 40–50% or higher. In adult ALL, however, progress in the development of effective therapy has been considerably slower. Recent large multicenter trials have shown CR rates of 60–80% in adult ALL patients, with long-term survival in only 15–30% of CR patients [3].

In the mid-1980s, induction therapies for childhood ALL commonly included vincristine (VCR), prednisolone (PSL), and *L*-asparaginase [9, 17]. When similar regimens were used in adults, only half of the patients responded

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completely. At that time the efficacy of anthracycline in the therapy of adult ALL had been reported and generally accepted [5]. Nonetheless, the combination effect of *L*-asparaginase and anthracycline was not clear.

The present long-term study was begun in 1983, to clarify the role of *L*-asparaginase in combination therapy with doxorubicin (Adriamycin, ADM), VCR and PSL for adult ALL. Preliminary reports of the results have already been published [14, 15], and we now report the final results and conclusions.

Patients and methods

Patient population

Between April 1983 and March 1985, 198 patients with ALL [French-American-British (FAB) classification L1 and L2] were enrolled in this study at 58 institutions located throughout Japan. Though the L3 subtype was not deliberately excluded, no case was registered. Eligible patients were between 15 and 65 years old with no prior treatment, no significant cardiac, renal, or hepatic concomitant disease, and no other malignancy. All enrollments were made with the informed consent of the patient and/or guardian.

The initial diagnosis of ALL was made at each institution in hematological samples, by morphological Wright's or May-Grünwald-Giemsa staining and by special cytochemical staining with agents such as peroxidase and/or Sudan Black B. The hematological specimens of peripheral blood and bone marrow were also sent to an extramural FAB classification committee (Chairman: Dr. Ichita Amaki, formerly Professor of the First Department of Internal Medicine, Nihon University School of Medicine) for confirmation of the FAB subtype diagnosis. Patient randomization was conducted by the Central Office of the Japanese Foundation for Multidisciplinary Treatment of Cancer.

Treatment protocol

The AdVP regimen consisted of: ADM (20 mg/m^2, i.v.) on days 1, 2, and 3 and optionally on days 15, 16 and 17; VCR (1.4 mg/m^2, max. 2 mg, i.v.) on days 1, 8, 15, and 22; and oral PSL (40 mg/m^2) on days 1 through 28. Minor modifications of the ADM dose, and cancellation of ADM administration on days 3, 15, 16 and 17 were permitted in accordance with the patient's condition and response. The L-AdVP regimen consisted of ADM (20 mg/m^2, i.v.) on days 1, 2, and 3; VCR (1.4 mg/m^2, max. 2 mg, i.v.) on days 1, 8, 15, and 22; oral PSL (40 mg/m^2) on days 1 through 28; and *L*-asparaginase (4000 IU/m^2) by 4-h drip infusion on days 15 through 28. Minor modification of the ADM dose was permitted, depending on the patient's condition. Adjustment of the *L*-asparaginase dose in the range of 3000–5000 IU was permitted, as was cancellation of *L*-asparaginase administration in accordance with its adverse effects or the patient's clinical status. All patients in both arms were to receive VCR and PSL for at least the 4-week period.

The consolidation therapy regimen, for patients who had attained complete remission (CR) in either arm of the induction therapy, consisted of two courses of: ADM (20 mg/m^2, i.v., days 1 and 2), VCR (1.4 mg/m^2, max. 2 mg, i.v., days 1 and 8), cyclophosphamide (CPM; 550 mg/m^2, 2-h drip infusion, days 1 and 8), methotrexate (MTX; 30 mg/m^2, i.v., days 1 and 8); and PSL (40 mg/m^2, p.o., days 1–14); with 20 Gy of cranial radiation and 3 doses of intrathecal MTX (10 mg/m^2) in the interim between the two cycles. After consolidation, all CR patients were treated as outpatients for 2 years or more with maintenance therapy consisting of successive repetitions of: 10 weeks of weekly MTX (15 mg/m^2, i.v.) and daily 6-mercaptopurine (6MP; 70 mg/m^2, p.o.); 2 weeks' intermission; 2 weeks of VCR (1.4 mg/m^2, 2 mg max., days 1 and 8), CPM (550 mg/m^2, 2-h drip infusion, days 1 and 8), 6MP (70 mg/m^2, p.o., days 1–14), and PSL (40 mg/m^2, p.o., days 1–14); and 2 weeks' intermission. The dose and administration schedule were adjustable, in accordance with the patient's hematological condition.

Analytical method

Chemotherapeutic effects were evaluated by Kimura's criteria [11], with CR defined by normocellular bone marrow containing normal erythroid and granuloid series with less than 5% lymphoblasts, accompanied by normal levels of peripheral white blood cells (WBC) and platelet counts with no circulating blasts. Partial remission (PR) was defined by lymphoblast reduction in bone marrow to less than half the percentage observed at the initiation of therapy, and in peripheral WBC to less than 5%. Relapse was defined by lymphoblasts in a bone marrow smear that exceeded 5% or presence in a peripheral blood smear, or detection of lymphoblast invasion of the central nervous system (CNS) or other sites.

DFS was defined as the time from CR to leukemic relapse or to death in CR, and duration of survival as the time from diagnosis to death. If the patient received allogeneic or autologous bone marrow transplantation (BMT), DFS and total survival time were censored at the time of BMT.

Statistical analysis

DFS and survival curves were calculated by the Kaplan-Meier estimate. The chi-square test was applied for statistical analysis of patient characteristics, remission rates and frequency of adverse effects. The generalized Wilcoxon test (GW) and log-rank test (LR) were used for statistical analysis of DFS and duration of survival. Statistical analyses were carried out at the Nagoya University Computation Center. The closing date for statistical evaluation was 31 March, 1991.

Results

Evaluable patients

Of the 198 patients enrolled, 166 were evaluable. The reasons for the 32 dropouts were as follows: major protocol violation, 8 (2 in AdVP, 6 in L-AdVP); early death (within 7 days), 4 (3 in AdVP, 1 in L-AdVP); misdiagnosis, 4 (4 in AdVP, 0 in L-AdVP; prior therapy, 3 (0 in AdVP, 3 in L-AdVP); other causes, 13 (7 in AdVP, 6 in L-AdVP). The incidence of misdiagnosis in the AdVP group was statistically higher than in the L-AdVP group ($P = 0.046$); none of the other causes showed any significant deviation between the two arms.

The FAB morphological diagnosis of 159 of the evaluable cases was confirmed by the extramural FAB classification committee, and statistical analysis concerning subtypes was restricted to these 159 cases.

A profile of all the evaluable patients at entry is given in Table 1. As shown, the median ages of patients in the AdVP and L-AdVP arms were 33 and 36 years, respectively. There was no significant difference between subjects in the two arms in age, sex, peripheral WBC count or FAB classification or in other characteristics (data not shown), such as red blood cell count, platelet count, findings of bone marrow analysis and blood chemistry.

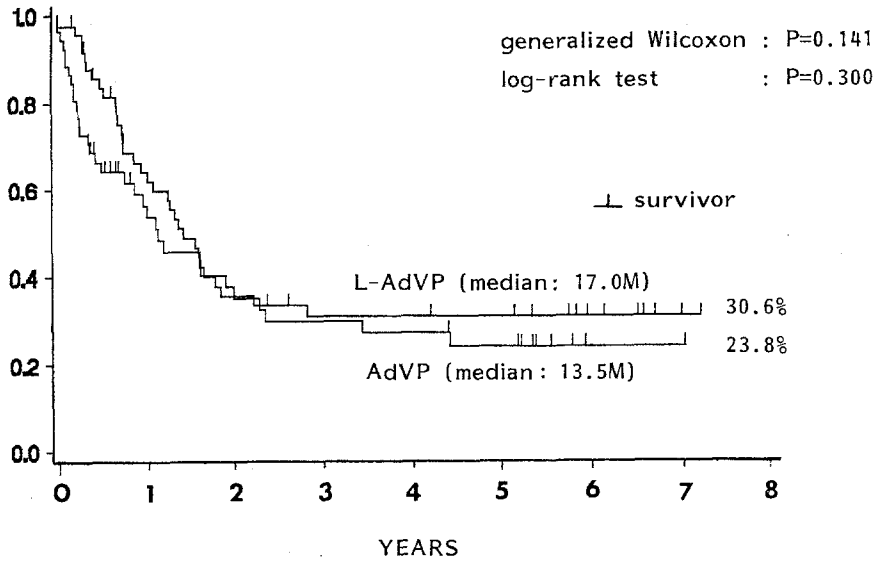

Fig. 1. Disease-free survival following complete remission

Table 1. Comparison of patient characteristics

	AdVP	L-AdVP
No. of entered cases	100	98
No. of evaluable cases	84	82
Age (years)		
15–19	21	15
20–29	17	12
30–39	14	17
40–49	18	22
50–59	11	14
60–65	3	2
(Median)	(33)	(36)
Male/female	50/34	46/36
WBC (x10^4/μl)		
–0.99	37	41
1.00–2.99	11	19
3.00–4.99	14	7
5.00–	22	15
FAB classification[a]		
L1	40	43
L2	42	34

[a]As confirmed by extramural FAB Classification Committee

Table 2. CR rates by FAB subtype

	AdVP	L-AdVP	Overall[a]
L1	32/40 = 80.0%	31/43 = 72.1%	63/83 = 75.9%
L2	20/42 = 47.6%	19/34 = 55.9%	39/76 = 51.3%

[a] CR rate statistically higher in L1 subtype than in L2 subtype ($P = 0.001$)

For the 166 evaluable cases, the median doses (range) of ADM and VCR during the induction therapy were 120 mg (30–240 mg) and 8.0 mg (2.0–21.0 mg) in the AdVP arm and 90 mg (30–240 mg) and 8.0 mg (2.0–21.0 mg) in the L-AdVP arm, respectively. Percentages of patients who were treated by the median or a less than median dose of Adriamycin were 67% in AdVP and 86% in L-AdVP, respectively. The median duration of *L*-asparaginase therapy was 14 days, with a range of 5–22 days (5–6 days, 10%; 7–10 days, 23%; 11–14 days, 60%; 15–22 days, 7%).

Ten patients in the AdVP arm and six in the L-AdVP arm received a BMT.

Response and survival

CR and PR were attained, respectively, in 53 (63.1%) and 9 of the 84 evaluable cases in the AdVP arm, and in 53 (64.6%) and 14 of the 82 evaluable cases in the L-AdVP arm, with no statistically significant difference between the two arms ($P = 0.837$). Median days to CR were 31 days (13–100) for AdVP and 37 days (19–88) for L-AdVP.

We did not designate a fixed salvage therapy for the patients who showed PR or no response to the induction therapy. Among the 23 refractory cases, there were 5 CRs among 16 patients with AdVP and 2 CRs among 7 patients with L-AdVP. One of the patients who achieved CR with the AdVP regimen was still living more than 5 years later. However, 42% of refractory cases in AdVP and 45% in L-AdVP had no opportunity of a second induction therapy.

The CR rates by confirmed FAB subtype are summarized in Table 2. In both treatment arms, the CR rate was higher for the L1 subtype than for the L2. The combined CR rate in both arms was accordingly higher for the L1 subtype.

DFS curves for all evaluable cases are shown in Fig. 1. The median DFS and 7-year DFS rate were 13.5 months and 23.8% with AdVP and 17.0 months and 30.6% with L-AdVP. Despite these differences, no statistical difference was found between the DFS curves for the two arms [$P = 0.141$ (GW), $P = 0.300$ (LR)]. The expected long-term DFS rates in evaluable cases were calculated as 15.0% for AdVP and 19.8% for L-AdVP. The causes of death in CR patients were all disease- or therapy-related. Figure 2 shows the duration of survival for all evaluable cases. The median time and 7-year survival rate were 12.7 months and 21.2%

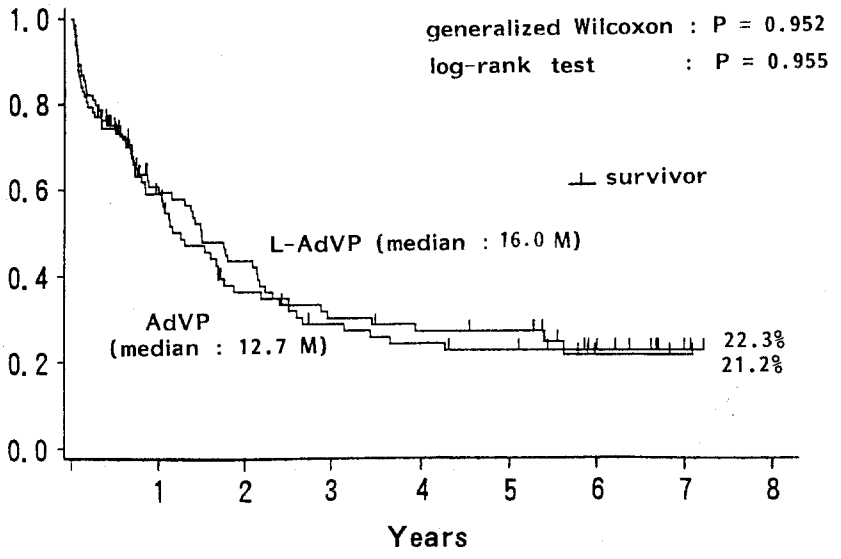

Fig. 2. Duration of survival for all evaluable cases

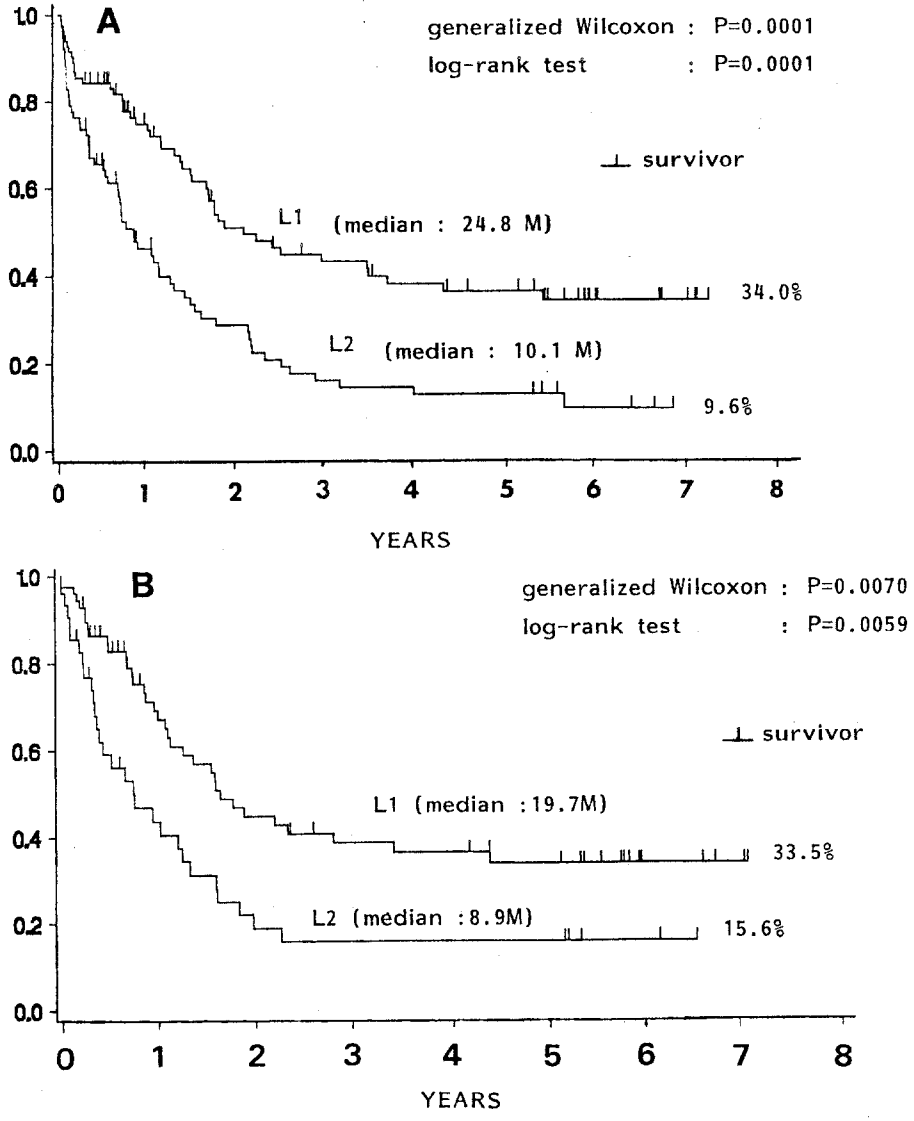

Fig. 3. A Duration of survival for FAB subtypes. B Disease-free survival for FAB subtypes

with AdVP, and 16.0 months and 22.3% for L-AdVP [$P = 0.955$ (GW), $P = 0.952$ (LR)].

Among all morphologically confirmed cases, both DFS and duration of survival were significantly longer for the L1 subtype than for the L2. As shown in Fig. 3A, the median duration of survival was 24.8 months for subtype L1 and 10.1 months for subtype L2, with a highly significant statistical difference between the two survival curves [$P = 0.0001$ (GW), $P = 0.0001$ (LR)]. As shown in Fig. 3B, the median DFS was 19.7 months for subtype L1 and 8.9 months for subtype L2, and the statistical difference between their DFS curves was also highly significant [P = 0.0070 (GW), P = 0.0059 (LR)]. Within the L1 or L2 subtype, however, there was no statistical difference between the two arms in DFS and duration of survival (data not shown).

The most common adverse effects observed in both treatment arms during induction therapy were anorexia, nausea, vomiting and elevation of GPT. Pancreatitis was significantly higher in L-AdVP than in AdVP (6.2%; 0%) ($P = 0.039$). One patient who had achieved PR was reported to have died because of liver toxicity of *L*-asparaginase. The incidences of hyperbilirubinemia of more than 2 mg/dl (27%; 18%), diabetes mellitus (22%; 17%), and diarrhea (17%; 7.7%) ($P = 0.059$) were somewhat higher in the L-AdVP arm than in the AdVP arm, but no statistically significant difference was found between the two arms with respect to these or other adverse effects.

Discussion

L-Asparaginase has been shown to have a unique enzymatic antitumor effect [9]. Although the efficacy of *L*-asparaginase in inducing remission of ALL has been previously reported, most studies had been performed in childhood disease [17]. In several clinical trials using *L*-asparaginase in adult ALL in the induction phase other drugs such as VCR, ADM or PSL were given simultaneously. This obscured the true impact of *L*-asparaginase in the treatment strategy for adult ALL [7, 13]. Memorial Sloan-Kettering Cancer Center (MSKCC) has reported a series of clinical studies using multidrug induction therapy, which included *L*-asparaginase in the late phase of consolidation. The late administration of *L*-asparaginase did not cast any light on its effectiveness in the early remission phase or during the entire period of DFS [8, 19].

Our trial was aimed at determining the clinical role of *L*-asparaginase in the induction phase of adult ALL. In the present study, there were 53 CRs and 9 PRs among 84 patients in the AdVP arm, and 53 CRs and 14 PRs among 82 patients in the L-AdVP arm. Although the median dose of ADM for the L-AdVP arm (90 mg) was slightly lower than that of the control arm (120 mg), these results showed that the addition of a single course of *L*-asparaginase contributed little to increasing the number of CRs. This suggests that *L*-asparaginase did not play a significant role in the achievement of CR in the multidrug combination schedule.

Our preliminary reports predicted that the addition of *L*-asparaginase might extend the DFS time for longer than the AdVP regimen alone [14, 15]. Although 7-year follow-up of the trial showed some additional antileukemic effects of *L*-asparaginase, this failed to achieve statistical significance. In our trial, all patients who attained CR have been followed up using the same treatment schedule. Although it might be possible that repeated administration of *L*-asparaginase could prolong the duration of CR, our data indicate that a single course of *L*-asparaginase could not prolong the DFS time significantly.

Several controversial results have been reported with FAB subtype correlated with prognosis. Leimet et al. reported that patients with the L1 subtype had a higher CR rate and a longer period of remission and survival than those with the L2 subtype, but that the prognostic influence of FAB subtype on remission time was lost when patient age was considered concurrently [12]. In contrast, Brearley et al reported no correlation between FAB morphology and either the rate or the duration of remission in 54 adult patients with ALL [2]. In a retrospective analysis, Baccarani et al. reported that patients with L1 and L2 subtype showed comparable survival times [1]. The Southwest Oncology Group, using a regimen identical to the L-10 M regimen of MSKCC, reported that the L1 subtype showed a slightly higher remission rate and a longer relapse-free survival time than were attained by the L2 subtype, but with no statistical significance [8]. It might not be easy to make a definite conclusion from these data because of the heterogeneity of the patients in age distribution, immunological phenotype, cytogenetical abnormalities, and contents of therapy. However, these clinical data suggest that patients with the L1 subtype may have a better prognosis than those with the L2 subtype, with a statistically marginal difference. Our data favored a better prognosis for the L1 subtype than for the L2 subtype. They also indicated that *L*-asparaginase did not potentiate an additional antileukemic effect on the L2 subtype. Further clinical data and multivariate analyses would be necessary for a clearer conclusion.

L-Asparaginase is known to cause several unpleasant adverse effects. The present trial showed that the addition of *L*-asparaginase subsequent to the combination chemotherapy brought about pancreatitis in 6.2% of cases, and 1 case of fatal liver toxicity. We also observed a higher occurrence of hyperbilirubinemia of more than 2 mg/dl, diabetes mellitus, diarrhea, DIC, hypofibrinogenemia and pancreatitis during the induction chemotherapy, but with no statistical significance. Activation of the coagulation system was reported recently in relation to the mechanism of hypercoagulability during treatment with *L*-asparaginase, but no hemostatic data were reported in detail [6,18]. No case of hyperlipidemia was reported in our trial [4, 16].

Recently, monomethoxypolyethylene glycol-conjugated *L*-asparaginase, a modified compound of *L*-asparaginase, was developed in an effort to reduce the toxicity of *L*-asparaginase. It lacks antigenicity and immunogenicity but retains catalytic activity as well as slow clearance in an experimental animal model. Clinically, it was repeatedly administered in a smaller dose than the *L*-asparaginase dose generally given without hypersensitivity or significant adverse effects [10]. Further clinical investigation of this drug

might help overcome the current therapeutic limitations of *L*-asparaginase.

These results suggest that a single course of *L*-asparaginase is not likely to act synergistically with ADM, VCR, and PSL in remission induction in adult ALL.

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Appendix

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