Analysis of 20-Year Follow-up Study of LVP Regimen for Adult Acute Lymphoblastic Leukemia

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Received January 17, 2001; received in revised form April 3, 2001; accepted April 9, 2001

Abstract

In an attempt to develop a new intensive chemotherapy for adults with untreated acute lymphoblastic leukemia (ALL), 3 sequential programs were designed for 62 patients (age range, 15 to 74 years; median age, 32 years) consisting of the L VP-79 (1979-1984, 27 patients), L VP-85 (1984-1986, 14 patients), and L VP-87 (1987-1989, 21 patients) regimens. The influence of clinical and biologic characteristics on the patient outcome was also examined. L-asparaginase (L-asp), vincristine, and prednisolone, defined collectively as L VP, were administered for induction chemotherapy in all protocols. After achieving complete remission (CR), patients underwent 2 years of multi-agent consolidation, intensification, and maintenance therapy consisting of various combinations. No significant differences were noted between the 3 groups regarding CR rate or survival. In total, 47 of 62 patients (75.8%) achieved CR. The median overall survival (OS) and median CR durations were 550 days and 341 days, respectively. Overall, the estimated survival rate at 20 years was 18.1%. The disease-free survival rate at 20 years was 26.2%. According to univariate analysis, the most favorable pretreatment characteristic for achieving CR was age. A younger age (<40 years of age), platelet count >50 × 10^9/L, having L1 morphology (French-American-British [FAB] classification subtype), female sex, and the absence of chromosomal abnormalities also helped improve survival rate. According to multivariate analysis, presence of Ph chromosome was found to be a major influencing factor for OS. Although higher doses of L-asp were administered than those used in previous studies, the adverse effect of L-asp was rarely identified. Therefore, it should be considered one of the key drugs for treatment of adult ALL. Further strategies still need to be developed to obtain better survival in adult ALL. Int J Hematol. 2001;74:157-164.

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Key words: Chemotherapy; Acute lymphoblastic leukemia; L-asparaginase; Prognostic factor; Ph chromosome

1. Introduction

The therapeutic approach in adult acute lymphoblastic leukemia (ALL) patients remains to be standardized. Recent treatment strategies for ALL have focused on intensive induction and postremission treatment with multiple chemotherapy agents as well as analyses of prognostic factors. Although these intensive chemotherapies have shown that 65% to 85% of patients with adult ALL achieve a complete remission (CR), the remission duration is still disappointingly short [1-12].

L-asparaginase (L-asp) is widely used for the treatment of child ALL with satisfactory results, although the agent is not often administered to adults with ALL. We designed 3 sequential protocols using L-asp, vincristine (VCR), and prednisolone (PSL), collectively known as LVP for adult ALL patients, with higher doses of L-asp than those used in previous studies. The consolidation and intensification of these protocols consisted of multiple courses of intensive chemotherapies in various combinations. The program was managed between 1979 and
1989. The efficacy and prognostic factors of this 20-year follow-up study for l-asparaginase–based regimens are reported.

2. Patients and Methods

2.1. Patients

Between June 1979 and October 1989, 62 previously untreated adult ALL patients (age, ≥14 years) were sequentially entered into the LVP chemotherapy schedules (age range, 14 to 74 years; median age, 32 years). All patients showed adequate cardiac, renal, and hepatic functions with no other malignancy. The diagnosis of ALL was confirmed by blood smears and bone marrow (BM) specimens for cytologic and cytochemical features according to the French-American-British (FAB) criteria [13,14]. Immunophenotypic analysis could not be done well at the time of diagnosis. A profile of patients is summarized in Tables 1 and 2. The analysis could not be done well at the time of diagnosis. A profile of patients is summarized in Tables 1 and 2. The patients were followed until December 31, 1999, after a median follow-up period of 5444 days (range, 91-7472 days).

2.2. Treatment Protocols

A total of 62 patients were enrolled in 3 sequential programs consisting of the LVP-79 (1979-1984, 27 patients), LVP-85 (1984-1986, 14 patients), and LVP-87 (1987-1989, 21 patients) regimens. The drugs and dosages used in the induction, consolidation, and maintenance phases of treatment are shown in Figure 1. The use of L-asp in these protocols was earlier and more extensive than that commonly used in adult ALL treatment programs [3,6,7,9,10]. The schema of these protocols consisted of induction therapy with LVP, consisting of L-asp (7000 U/m²) by 4-hour drip infusion, VCR (1.4 mg/m²; maximum dose, 2 mg) intravenously (IV), and oral PSL (40 mg/m²), followed by early intensive consolidation as detailed in Figure 1. Almost the same LVP induction protocols were used in all 3 programs, although the consolidation regimens were different for each program. In LVP-79, 2 courses of LVP were followed by 1 course of doxorubicin (ADR) (25-30 mg/m² IV) + cytosine arabinoside (AraC) (70 mg/m², drip infusion) + cyclophosphamide (CY) (700 mg/m², 2-hour drip infusion) + 6-mercaptopurine (6MP) (70 mg/m² orally) + PSL (35 mg/m² orally); this drug regimen is also known as ACCMP. Because relapses were observed during the 2 courses of LVP consolidation therapy in the LVP-79 protocol, the third course of LVP was replaced by a more intensive consolidation therapy in the later protocols. In LVP-85, 1 course following each consolidation therapy was used; this regimen consisted of daunorubicin (DNR) (35 mg/m² IV) + AraC + CY + 6MP + PSL (DCCMP); VCR + methotrexate (MTX) (15 mg IV) + 6MP + PSL (VMMC); and l-asparaginase + DCCMP (LDCCMP). DNR was substituted for ADR because the response rate and remission duration for ALL were similar for these 2 agents [1,2,4-11,15]. In LVP-87, ACCMP and LVP + MTX (150 mg, drip infusion) were administered followed by ADR + AraC + 6MP + PSL (ACMP). The maintenance and intensification protocols consisted of 2 courses of VCR + CY + 6MP + PSL (VCMP) and 1 course of LACCMP (LVP-79 and LVP-87) or LDCCMP (LVP-85) for all patients. These treatments were repeated every 5 to 6 weeks and continued for 2 years. No special prophylaxis was administered to prevent the adverse effects of L-asp. A central nervous system (CNS) prophylaxis was performed using 15 mg of MTX intrathecally.

All patients were hospitalized during the induction treatment period. No hematopoietic growth factors were used. The use of oral antibiotics (amphotericin B and polymyxin B or ciprofloxacin) was mandatory when the neutrophil count was less than 0.5 × 10⁹/L. The management of febrile episodes was performed by the administration of intravenous antibiotics. Packed red blood cells and platelet transfusions were administered when needed.

2.3. Criteria for Response

The patients were considered to be in CR when the neutrophil count was greater than 10×10⁹/L, the results of a BM examination were normal including fewer than 5% blasts with normal cellularity, and all extramedullary diseases had subsided. Relapse was defined by the presence of >5% lymphoblasts in a BM smear or the detection of lymphoblast invasion at any site of the body, including the peripheral blood.

2.4. Statistical Analysis

The final analysis of these patients was performed on December 31, 1999.

The chi-square method was applied to identify the relationships between the patient characteristics, remission rates,

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### Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>LVP-79</th>
<th>LVP-85</th>
<th>LVP-87</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>62</td>
<td>27</td>
<td>14</td>
<td>21</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>34/28</td>
<td>15/12</td>
<td>6/8</td>
<td>13/8</td>
</tr>
<tr>
<td>Age, y, median (range)</td>
<td>32 (14-74)</td>
<td>38 (15-74)</td>
<td>30 (17-50)</td>
<td>26 (14-62)</td>
</tr>
<tr>
<td>FAB (L1/L2)</td>
<td>39/23</td>
<td>13/14</td>
<td>10/4</td>
<td>16/5</td>
</tr>
<tr>
<td>Initial platelet count, ×10⁹/L, median (range)</td>
<td>46 (3-473)</td>
<td>33 (3-361)</td>
<td>48 (7-237)</td>
<td>80 (9-473)</td>
</tr>
<tr>
<td>Initial leukocyte count, ×10⁹/L, median (range)</td>
<td>32 (1-57)</td>
<td>32 (3-57)</td>
<td>35 (2-58)</td>
<td>36 (1-57)</td>
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Chromosomal analysis

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<tr>
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<th>LVP-85</th>
<th>LVP-87</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
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<td>9</td>
<td>10</td>
</tr>
<tr>
<td>Ph⁺</td>
<td>9</td>
<td>6</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Other chromosomal abnormality</td>
<td>6</td>
<td>2</td>
<td>1</td>
<td>3</td>
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</table>

*LVP indicates L-asparaginase + vincristine + prednisolone; FAB, French-American-British classification; Ph, Philadelphia chromosome.*