Relapsing Process in FAB Subtypes of Adult Acute Leukemia and Its Relationship to Treatment Regimens

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AMAKI, I., OHSHIMA, T., TAKEO, H., TAKEUCHI, J., HORIKOSHI, A., HAYAKAWA, Y., MURAKAMI, J., SAKURAI, T. AND KAWAMURA, M. Relapsing Process in FAB Subtypes of Adult Acute Leukemia and Its Relationship to Treatment Regimens. Tohoku J. exp. Med., 1986, 148 (4), 449-458 —— The relapsing process in the bone marrow was studied in those 77 patients with adult acute leukemia, diagnosed according to the FAB classification who achieved complete remission (CR) and then received intermittent multi-drug intensification treatment. Relapse occurred in most of the patients who exhibited Auer rods or Ph1 chromosomes in the bone marrow, or in whom blasts increased to 8% or more, but some patients remained in CR by subsequent treatment, that is, relapsing process was reversible. With our conventional treatment, the relapse or relapsing process occurred in most of the patients with L1, L2 and M1 subtypes within 6 months and was irreversible. It occurred mainly between 5 and 13 months in those with M2, M3 and M5 and was reversible in some cases. Patients with M4 subtype received intensified treatment due to the difficulty of achieving remission; relapse was seen in only 3 of 7 cases. To prevent relapse and attain a potential cure, the treatment should be intensive before the relapsing process with adequate supporting care. In view of the above-mentioned observations, our new treatment protocols for acute leukemia were designed to be more intensive than those conventionally employed, and to be discontinued within approximately 10 months in lymphoblastic leukemia and approximately 8 months in myeloid leukemia. ——— acute leukemia; relapsing process; FAB classification; early intensive treatment

Since the complete remission (CR) rate in the treatment of acute leukemia has reached 70% in general, the next aim is to prevent the relapse of the disease. Although the onset of relapse in acute leukemia is recognized as a fall in the CR probability curve, the process of relapse and the effects of treatment on it are not obvious from the curve. Before relapse occurs in the course of acute leukemia, there should be some indications such as a slight increase in blasts or the appear-

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... of Auer rods in the bone marrow. Is it possible to prevent relapse in this disease phase or should the treatment be given earlier than that? In other words, how should we monitor the quality of CR and prevent relapse? In this study we observed the process of relapse in the bone marrow in the course of treating a total of 77 patients with adult acute leukemia. We also observed the influence of treatment on the relapsing process to evaluate the quality of CR retrospectively. Moreover, we observed complications involving the central nervous system (CNS) and extramedullary tumor formations to consider the possibility of preventing these manifestations of relapse.

**Patients and Methods**

*Patients and treatments.* The subjects consisted of 77 patients with adult acute leukemia, 22 lymphoblastic and 55 myeloid according to the FAB classification (Amaki et al. 1984), who were referred to our department between January, 1978 and June, 1983, and who had received intermittent multi-drug intensification treatment for 2.5 years after achieving CR. The treatment of lymphoblastic leukemia was given with the LVP regimen (Fig. 1) (Ohshima et al. 1980), but the induction therapy had been carried out with vincristine and prednisolone until June, 1979. As a prophylactic treatment for CNS leukemia, 15 mg of methotrexate was intrathecally injected 6 times over a 3-week period immediately after the CR.

Myeloid leukemia was mainly treated with the BH-AC • DMP regimen (Yamada et al. 1980) and daunorubicin injections were often added, using cellularity and the percentage of blasts in the marrow as indices, so that aplasia of the bone marrow was attained in about 10 days. Heparin was given to M3 patients and daunorubicin was administered every day until aplasia was recognized with the same treatment regimen. Until April, 1979, however, the DCMP two step regimen (Cooperative Study Group. 1978) had been used instead of the BH-AC • DMP. For consolidation and intensification of CR, an alternative treatment with BH-AC • DMP and VEMP (vincristine, cyclophosphamide, 6MP and prednisolone) was used for 2.5 years after complete remission (Fig. 1).

![Fig. 1. LVP regimen for adult lymphoblastic leukemia](image)

1) Maintenance therapy is repeated for 2.5 years after complete remission.
2) At present daunorubicin 35 mg/m² is used instead of ADR.
conducted until 1980; but, as relapse seemed to be more frequent after the VEMP regimen, only BH-AC • DMP was given every 6 weeks thereafter (Fig. 2). Prophylactic treatment for CNS leukemia was not performed initially. After the beginning of BH-AC • DMP, however, the CNS relapse seemed more frequent than in the DCMP two-step regimen. Intrathecal injections of ara-C (60 mg) have been performed 3 times after the CR since 1981.

Methods. The relapsing process in patients with various subtypes of adult acute leukemia is illustrated in Figs. 3 to 8. C in the figures indicates CR with less than 5% blasts; the percentage of blasts gradually increases with the relapsing process. E is the stage exhibiting 8% or more blasts and F 15% or more blasts. The latter was defined as relapse in this study, because relapsing process was usually irreversible at this point. D represents the appearance of Auer rods or abnormal chromosomes, such as Ph1, with less than 8% blasts. D and E were considered to be the beginning stages of the relapsing process. G shows the deaths from leukemia, including deaths from bleeding and infections. Death without leukemic relapse is shown with a + at the end of the curve. The CNS manifestations and extramedullary tumor formations are shown with open and closed circles on the curve, respectively. Off-therapy is indicated by a triangle and resumption of treatment by an asterisk. Re-attainment of CR was not illustrated when its duration was short. Lymphoblastic leukemia patients over 40 years old and myeloid leukemia patients over 50
Results

Lymphoblastic leukemia

The relapsing process in the bone marrow of 11 patients of the L1 subtype is shown in Fig. 3. Eight patients relapsed: 4 within 6 months from the attainment of CR, 3 within 12 months and 1 at slightly over 12 months. One patient died at 6 months after consolidation treatment. Two patients have been in continued complete remission (CCR) for more than 4 years. They were 15 and 19 years old.

The relapsing process in the bone marrow of 11 L2 patients is shown in Fig. 4. Relapse occurred in 7 patients: 5 within 6 months and 2 within 9 months. Three patients have been in CCR for more than 4 years and all of them are off therapy. One patient died after the intensification treatment at 2.5 years without relapse. In one of the patients with a long CCR, the blasts in the bone marrow...
reached 8% at 7 months; after the intensification treatment, however, they decreased to the normal level without a subsequent increase. No patients over 40 years old had a long CCR.

CNS involvement during bone marrow remission was seen in one case of L1 and two cases of L2, and these cases later exhibited relapse in the bone marrow.

**Myeloid leukemia**

The relapsing process of 11 M1 patients is depicted in Fig. 5. Relapse occurred in 2 cases within 6 months and in 3 within 8 months. Three patients died within 9 months without relapse due to the adverse effects of post-remission chemotherapy. They were all over 50 years old. One patient suffered from CNS involvement but the treatment was impossible because of liver dysfunction. He died of cirrhosis of the liver without relapse of leukemia. Only one patient had a long CCR. This patient was off therapy after 3 years 8 months, but at 4 years 3 months, Auer rods appeared for 2 months, and then disappeared after the treatment with BH-AC • AMP (BH-AC, acrasinomytin, 6MP and prednisolone). They appeared again at 5 years 6 months, and also at 5 years 9 months; after 6 years the percentages of blasts in the bone marrow were 8.6, 9.6 and 7.4%. They disappeared, however, and the percentage of blasts returned to normal after the intensification with BH-AC • DMP. The patient has remained in CR for 7 years.

The relapsing process in the bone marrow of 26 M2 patients is shown in Fig. 6. Relapse occurred in 17 cases and its onset was clearly later than that of M1. No relapse occurred until 6 months; 10 patients relapsed between 6 and 12 months, and 4 between 12 and 24 months. There were three patients who relapsed after 2 years; in one, blasts in the bone marrow increased to 28% at 2 years 6 months, but soon returned to normal after the treatment. Relapse subsequently occurred again at 3 years 8 months. In another patient in whom Auer rods were detected without an increase in blasts, at 1 year 10 months for 4 months, at

![Fig. 6](image_url)  
**Fig. 6.** Relapsing process in bone marrow. FAB subtype M2 (n = 26)
3 years 1 month and at 3 years 10 months, relapse was seen at 4 years 2 months. In one patient, Auer rods appeared once at 8 months, but disappeared soon; after the patient was off therapy at 2 years 9 months, they appeared again at 3 years 9 months. Thus, treatment was begun, and after they disappeared, no sign of the disease was observed, and therapy was discontinued. In one patient, Ph¹ chromosomes were found in the bone marrow at 6 months. These disappeared soon thereafter, but after 3 years they reappeared for 4 months, then again disappeared; the patient has been off therapy and remained in CR for 5 years. After 3 years 8 of the 26 patients (30.8%) were in CR, and all were off therapy. CNS involvement during the CR in the bone marrow was observed in 6 patients for whom no prophylaxis was given, and in all these cases but one, bone marrow relapse occurred shortly thereafter. In the one remaining case, CNS involvement subsided after irradiation therapy and intrathecal injections. No CNS involvement was seen in the patients receiving prophylactic treatment. Extramedullary tumor formations occurred in 3 patients, 2 in the subcutaneous soft tissue and one in the

Fig. 7. Relapsing process in bone marrow. FAB subtype M3 (n = 8)

Fig. 8. Relapsing process in bone marrow. FAB subtype M4 (n = 7) and M5 (n = 3)
mammary gland. In these cases, relapse in the bone marrow was also noted at almost the same time.

The relapsing process in the bone marrow of 8 M3 patients is shown in Fig. 7. In 6 patients, relapse in the bone marrow occurred relatively late; in one case at 5 months, 2 within 12 months and 3 within 24 months. Two cases remain in CR for more than 4 years. One of these, a 50-year-old man, was diagnosed as having CNS involvement at 7 months, but after treatment he was considered recovered from CNS leukemia, although the treatment had been stopped due to liver dysfunction. He now suffers from paralysis of the legs because of demylinization. Another patient was off therapy at 2 years and 9 months and still remains in CCR for 4 years and 8 months.

The relapsing process in 7 M4 patients is shown in Fig. 8. Three of 7 cases relapsed at 3 months, 2 years 3 months and 3 years 2 months. In the last case blasts in the marrow retured to normal with treatment, but relapse occurred again at 6 years 2 months, and the patient died. CNS involvement was seen in 2 cases. Four of 7 (57.1%) patients have been in CCR after 4 years. One of these died of an accident. Prognosis was best for M4 in terms of the percentage of patients remaining in long CCR.

In three M5 patients the remission duration was nearly 6 months, nearly 1 year, and slightly over 2 years, with one case of CNS involvement, and relapsing process seemed to progress rather slowly (Fig. 8).

**DISCUSSION**

In our series, relapse of lymphoblastic leukemia occurred relatively early in both L1 and L2, and relapse occurred within 1 year in 7 of 11 (63.6%) patients, and in 8 of 12 (66.6%) patients, respectively, and the median remission durations in the relapsed cases were 6 and 5.2 months, respectively. Each relapsing process proceeded rapidly when once it occurred, showing the steep curves in Figs 3 and 4. The process was irreversible in all cases but one. In the one L2 case the blasts in the bone marrow increased to 8%, then, however decreased to normal with no increase thereafter. In general, the treatment should be intensive before the beginning of relapsing process. Short CCR is presumably due to the initial 3 courses of LVP regimen for the remission induction and consolidation treatment. The LVP regimen is adequate for remission induction of lymphoblastic leukemia, but resistant leukemia cells may more readily appear with this regimen. In patients completing ACCMP for consolidation and LACCMP for intensification (Fig. 1), relapse occurred only very rarely. We therefore, improved the protocol (Fig. 1) by reducing the courses of LVP regimen from 3 to 2 and switching to ACCMP and LACCMP regimens earlier than in the previous protocol. And we decided to discontinue the treatment within approximately 10 months.

The LVP regimen can achieve CR in about 70% of the patients with adult lymphoblastic leukemia, and when CR has been achieved, the bone marrow is not
suppressed by the regimen. In this situation, combinations of strong myelotoxic drugs such as ACCMP and LACCMP which have not been given to the patient can eradicate residual leukemia cells very effectively, and may be used relatively safely. Of the 2 patients with L1 and 3 with L2 who had long CCR, all patients were under 40 years old.

Although M1 and M2 subtypes are both myeloblastic leukemia and were treated similarly, the relapsing processes in the bone marrow varied considerably between these two subtypes.

Relapse occurred earlier in M1 patients: 5/11 (45.5%) within one year, the median remission duration of the 6 relapsed cases being slightly more than 6.5 months. Process of relapse was fast and the curves in Fig. 5 are steep. A long CCR was observed in only one patient (9.1%). In this M1 patient who was in CR for 4 years, Auer rods were detected (Grade I) and then the blasts in the bone marrow increased to Grade E (over 8%), but the bone marrow returned to normal after treatment, and he has remained in CCR.

Three M1 subtype patients died without relapse within 9 months due to the adverse effects of chemotherapy, all being over 50 years old.

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Three M1 subtype patients died without relapse within 9 months due to the adverse effects of chemotherapy, all being over 50 years old.

The relapse in M2 patients was late. No patient exhibited relapse within 6 months and the median remission duration in the relapsed cases was 11.6 months; relapse occurred even 3 years after the CR. There were 8 patients (30.8%) remaining in CR after 4 years indicating a good prognosis for this subtype. Two M2 patients with marrow Auer rods but without increased blasts (Grade D) relapsed afterwards, whereas other two patients whose marrow exhibited either Ph1 chromosomes or Auer rods without an increase in blasts (Grade D) remained in CR after treatment.

### Table 1. Relapse in FAB subtypes

<table>
<thead>
<tr>
<th>FAB subtype</th>
<th>Number of cases</th>
<th>Years to relapse from CR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>&lt;0.5</td>
</tr>
<tr>
<td>L1</td>
<td>11</td>
<td>4</td>
</tr>
<tr>
<td>L2</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td>Lymphoblastic</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>M1</td>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td>M2</td>
<td>26</td>
<td>0</td>
</tr>
<tr>
<td>M3</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>M4</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>M5</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Myeloid</td>
<td>55</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>77</td>
<td></td>
</tr>
</tbody>
</table>

* Died of accident 4 years 3 months after CR
mo, month; yr, year.
Relapsing Process in Acute Leukemia and Relation to Treatment

Relapse in M3 occurred late and the median remission duration of the 6 relapsed cases was 11.5 months. Two patients have remained in CCR for more than 4 years. The bone marrow did not return to normal following the relapsing process in any of the patients, that is the process was irreversible in this subtype.

The median remission duration of three M4 patients who had a relapse was 2.3 years. Because of the difficulty of achieving CR, the treatment was intensive for this subtype and 4 of 7 patients remain in CCR for more than 4 years, thus M4 subtype had the best prognosis in this sense.

All three M5 patients relapsed between 6 months and slightly more than 2 years. It appears to be difficult for M5 patients to remain in remission for long periods with the conventional treatments.

The relapse and relapsing process are fairly characteristic in each myeloid subtype, as the curves in Figs. 5 to 8 illustrate. A summary of the finding is shown in Table 1. Once relapsing process occurred, the prognosis of the patients became worse, even if it was reversible in some cases especially in M1, M2 and M4 subtypes. We consider that the treatment should be most intensive before the beginning of relapsing process, in the early stage of treatment, that is, in the first several months, under careful supporting therapies. This view has already been proposed by many hematologists from other standpoints (Weinstein et al. 1983; Cassileth et al. 1984; Vogler et al. 1984; Worsley and Galton 1984). Our new protocol for adult acute myeloid leukemia was designed to be most intensive in the early stage and to be discontinued within approximately 8 months.

<table>
<thead>
<tr>
<th>Median rem. duration in relapsed cases</th>
<th>Death without relapse</th>
<th>No relapse &gt;3 year after CR</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 mo</td>
<td>1</td>
<td>2 18.2%</td>
</tr>
<tr>
<td>5.2 mo</td>
<td>1</td>
<td>3 27.2%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5 22.7%</td>
</tr>
<tr>
<td>6.5 mo</td>
<td>4</td>
<td>1 9.1%</td>
</tr>
<tr>
<td>11.6 mo</td>
<td>1</td>
<td>8 30.8%</td>
</tr>
<tr>
<td>11.5 mo</td>
<td>0</td>
<td>2 25 %</td>
</tr>
<tr>
<td>2 yr 3 mo</td>
<td>1*</td>
<td>4 57.1%</td>
</tr>
<tr>
<td>11.8 mo</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15 27.2%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20 25.6%</td>
</tr>
</tbody>
</table>

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