Prognosis of Acute Myeloblastic Leukemia: Chromosomal Correlation

By Masaharu Sakurai and Avery A. Sandberg

A correlation was made between chromosomal findings in the marrow of AML patients obtained during the course of the disease, some of the clinical and cytologic features, and the survival span of these patients. The median survival time for each patient was obtained by the use of log-probability paper. Of the 69 patients with AML studied, 29 showed abnormal metaphases in the marrow at least once during the course of the disease (A-patients) and 40 did not (N-patients). In the former group, ten cases were never shown to have a normal metaphase (AA-patients), even upon repeated examinations, whereas the remaining 19 cases had at least one normal metaphase during the course of the AML (AN-patients). The median life-span for the A-patients was 8.0 mo and 11.5 mo for the N-patients. Among the former group, the AN-patients had a median life span of 10.3 mo and the AA-patients only 3.2 mo. A dissociation between the proportion of cells with chromosomal abnormalities and the cellular differential in the marrow suggested the appearance of the karyotypic changes in the later stages of the disease in some patients and the presence of such changes in both erythroid and myeloid cells in erythroleukemia. The results indicate the importance of the presence in the marrow of even one normal metaphase in the prognosis of AML and a possible correlation of AA-patients with acute erythroleukemia.

Controversy continues to exist concerning the role of chromosomal abnormalities in the causation and course of human acute leukemia. Whether these karyotypic changes play a direct and critical role in the initiation and promotion of acute leukemia or whether they are merely secondary phenomena, has been one of the problems to be elucidated in the study of the cytogenetics of acute leukemia.

Since it is impossible, at present, to ascertain with any degree of accuracy either the exact site of origin in the body of the acute leukemia or the time of onset of this disease, chromosomal analysis is not feasible at these critical

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points. Thus, cytogenetic studies in acute leukemia are possible only after the
disease is well established and evident and are directed towards a correlation
of the karyotypic findings with clinical and other parameters of acute leukemia,
with the hope of throwing light upon the relation of chromosomal changes in
the genesis, progression, classification, and response to therapy of acute leu-
kemia. Were the role of chromosomes during the course of leukemia estab-
lished, would it be possible to extrapolate, to some extent, their role in those
early stages of acute leukemia not subject to analysis?

In general, the clinical and cytologic picture in acute lymphoblastic leukemia
(ALL) tends to be more homogeneous than that in acute myeloblastic leukemia
(AML). In the latter group of acute leukemia are included acute erythro-
leukemia and possibly different forms of AML, i.e., myelomonoblastic and
monoblastic forms (Naegeli vs Schilling types?). Even though there is a
number of parameters which may differentiate one AML from another, includ-
ing cytologic and biochemical differences between the leukemic cells, through
an analysis of a large group of patients with AML it may be possible to
ascertain whether differentiation of the AML's can be made on the basis
of karyotypic findings. This was one of the aims of the study to be presented.

On the assumption that repeated examinations of the chromosome consti-
tution of acute leukemic cells may contribute to the clarification of some of
the problems raised above, we have analyzed the chromosomes of patients
with acute myeloblastic leukemia. The major points to which the study
addressed itself were: (1) Are there any differences in the clinical features
of AML between patients with and without chromosomal changes? (2) Do the
chromosomal abnormalities change during the course of AML and can these
changes affect or be associated with the clinical course of the disease?

MATERIALS AND METHODS

Bone marrow aspirates were obtained from the sternum or iliac crest of the patients
with AML hospitalized at or attending the clinics of RPMI.

Chromosome analyses were performed on bone marrow materials by a direct tech-
nique, though occasionally short term culture (16–18 hr) was resorted to, according to
previously described methods. Chromosomes of approximately 25 cells were usually
counted in each sample and every metaphase was carefully scrutinized under the micro-
scope. The presence of normalities or abnormalities in the metaphases were further
confirmed by examination of karyotypes. In those instances in which stem lines were
detected, cells were classified into those with abnormalities, those without abnormalities
(normal), and those unclear. In certain cases, the number of cells examined was enlarged
in order to make sure of the presence or absence of karyotypic abnormalities. There were
several samples in which only a small number of cells could be scored, because of
insufficient metaphases or a low mitotic index.

The cellularity of the bone marrow contents and a cellular differential count were
determined on the same marrow material on which chromosomal analysis was performed.
Five hundred marrow cells were usually analyzed.

The patients were divided into those with and without chromosomal abnormalities
(A-patients and N-patients), and the former were further divided into two subgroups
according to the presence or absence of normal (diploid) metaphases (AN-patients and
AA-patients). All patients in whom more than one normal metaphase was detected
during the course of the disease were classified as AN-patients.

The life span for each patient was calculated from the time of onset of symptoms. The
disease was empirically assigned to have begun on the 16th day of the month, when
the exact date was not available. The patients who are still living at the time of the writing of this paper were assumed to be still alive for another month after June 16, 1972 (none in the AA-group, two in the AN, and nine in the N). The median survivals were estimated by the use of log-probability paper.9

RESULTS

Of the 69 patients (previously unpublished) with AML investigated in the present study, 40 patients had no chromosomal abnormalities (N-patients) in the leukemic cells and 29 showed stem lines at least some time during the course of the disease (A-patients). In the latter group, 10 cases were never shown to be associated with normal karyotypes (AA-patients) and the remaining 19 cases were shown to have at least one normal metaphase in the marrow during the course of the acute leukemia (AN-patients). These data are shown in Table 1, including the distribution of the number of examinations performed.

The age distribution of the patients studied is shown in Figure 1. There was a mode in the 60–70 age group in the A-patients, whereas in the N-patients there was one in the 40–50 group, but a χ²-test revealed that the difference in the distribution was not significant.

The type of antileukemic chemotherapy received by the patients in the various groups did not differ materially from group to group, though it did change with different protocols at different times. Thus, most of the patients in the AA (9 out of 10), AN (18 out of 19), and N (38 out of 40) groups were given arabinosyl cytosine in combination with one or more of the following: thioguanine, CCNU or BCNU, cytoxan, vincristine or prednisone. One patient

<table>
<thead>
<tr>
<th>Patient Material</th>
<th>Total No. of Patients</th>
<th>Patients by Number of Marrow Chromosome Examinations</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with chromosomal abnormalities (A-patients)</td>
<td>29 (42%)</td>
<td>11</td>
<td>18</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with abnormal metaphases only (AA-patients)</td>
<td>10</td>
<td>7</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with abnormal and normal metaphases (AN-patients)</td>
<td>19</td>
<td>4</td>
<td>15</td>
<td>2</td>
<td>4</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients without chromosomal abnormalities (N-patients)</td>
<td>40 (58%)</td>
<td>16</td>
<td>24</td>
<td>6</td>
<td>7</td>
<td>5</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Total No. of patients</td>
<td>69</td>
<td>27</td>
<td>42</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>
Patients with Abnormal Metaphases (A-patients)

Patients without Abnormal Metaphases (N-patients)

Fig. 1. Age distribution of patients with AML according to chromosomal findings.

in the AA-group died before therapy could be given, one patient in the
AN-group received L-asparaginase, and two subjects in the N-group received
only prednisone and 6-MP. In all groups, however, most (>50%) of the pa-
tients were treated with a combination of arabinosyl cytosine and thioguanine.

The total and average numbers of cytogenetic examinations performed on
the patients and the average length of intervals between examinations are
shown in Tables 2 and 3. Of the 69 cytogenetic examinations performed on
the AN-patients, nine showed only abnormal and 24 only normal metaphases.
The average number of examinations was about the same in the A-patients
and N-patients, but among the former, the AA-patients had a lesser number of
examinations and a shorter average length of intervals between examinations.

In the present study, the presence and not the type of karyotypic abnormal-
ity was taken into account. In calculating the percentages of abnormal or
normal metaphases, unclear metaphases were disregarded. Since there was no
significant difference between the results obtained with direct or indirect
examinations in five AN-patients, in which both methods were applied at the
same time, data from both methods were treated equally, and for these cases
the average of percentages from both methods was utilized in the further
processing of data. Some of the average figures are given in Table 4 together
with those for N-patients. (Detailed clinical and cytogenetic data on the
patients presented may be obtained by writing to the authors.)

To obtain median survivals, the per cent cumulative mortality was plotted
against the number of months the patients survived on log-probability paper
(Fig. 2).

The median life spans for the various groups of patients are shown in
Fig. 2. The median survival for the A-patients as a group was shorter than that
for N-patients. Among the former, however, the AA-patients had a much
Table 2. Number of Cytogenetic Examinations of Marrow Material Classified According to the Presence of Abnormal and/or Normal Metaphases in Acute Myeloblastic Leukemia

<table>
<thead>
<tr>
<th>Patient Material</th>
<th>Total Examinations</th>
<th>Examinations in which Only abnormal Metaphases Were Found</th>
<th>Abnormal and Normal Metaphases Were Found</th>
<th>Only Normal Metaphases Were Found</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with chromosomal abnormalities (A-patients)</td>
<td>83</td>
<td>23</td>
<td>36</td>
<td>24</td>
</tr>
<tr>
<td>Patients with abnormal metaphases only (AA-patients)</td>
<td>14</td>
<td>14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with abnormal and normal metaphases (AN-patients)</td>
<td>69</td>
<td>9</td>
<td>36</td>
<td>24</td>
</tr>
<tr>
<td>Patients without chromosomal abnormalities (N-patients)</td>
<td>103</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total examinations</td>
<td>186</td>
<td>23</td>
<td>36</td>
<td>127</td>
</tr>
</tbody>
</table>

Shorter survival time than AN-patients and all AA-patients died within 5 mo. A t-test revealed that the difference for the former comparison was not significant; that for the latter, however, was highly significant (p<0.01).

When the median life span was calculated on the basis of whether abnormal chromosomal findings of any nature were present at the time of diagnosis or study and whether the presence or absence of any diploid (normal) metaphases at this particular point affected the prognosis, the following results were obtained: 12 patients with only abnormal metaphases had a median survival time of 3.6 mo, 13 patients with both abnormal and normal metaphases, 7.4 mo, and the 44 subjects with only normal metaphases, 12.5 mo. Thus, the survival time among the various groups was very similar to that calculated above.

The percentage of normal metaphases was plotted against the time interval between the examination and the patient's death (Fig. 3). Twelve out of 21 specimens devoid of normal metaphases were obtained within 1 mo and seven others within 5 mo prior to death. There was no apparent correlation

Table 3. Data on Cytogenetic Examinations in Patients with Acute Myeloblastic Leukemia

<table>
<thead>
<tr>
<th>Patient Material</th>
<th>Average No. of Examinations</th>
<th>Average Length of Intervals Between Examinations (Patients With Multiple Examinations)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with chromosomal abnormalities (A-patients)</td>
<td>2.9</td>
<td>54 days</td>
</tr>
<tr>
<td>Patients with abnormal metaphases only (AA-patients)</td>
<td>1.4</td>
<td>26 days</td>
</tr>
<tr>
<td>Patients with abnormal and normal metaphases (AN-patients)</td>
<td>3.6</td>
<td>56 days</td>
</tr>
<tr>
<td>Patients without chromosomal abnormalities (N-patients)</td>
<td>2.6</td>
<td>51 days</td>
</tr>
<tr>
<td>Total No. of patients</td>
<td>2.7</td>
<td>52 days</td>
</tr>
</tbody>
</table>
Fig. 2. The cumulative per cent of mortality among the various groups of patients with AML as plotted on log probability paper. The values were plotted as \( X + 2 \), where \( X \) is the number of months of survival and the 2 added for a better fit of the data. Arrows indicate the median survival.

between the percentage of normal metaphases and the length of time before death.

A correlation between the chromosomal findings and the number of cells present in the bone marrow of A-patients was attempted. The percentages of normal or abnormal metaphases were plotted against the percentages of pro-erythroblasts, erythroblasts, myelocytes plus mature granulocytes, or myeloblasts plus promyelocytes, respectively (Figs. 4 and 5).

As is apparent from Fig. 4, no correlation was found to exist between the percentage of abnormal metaphases and that of myeloblasts plus promyelocytes. However, in addition to the clusters at the upper right and lower left of the figure, representing cases in relapse and remission, respectively, there were two other clusters of cases at the upper left and lower right. The former cluster consists primarily of erythroleukemia cases (patients MK, WM, and FL) and the latter represents a separate group of patients with AML, in which chromosome abnormalities appeared for the first time in a later stage of the disease (patients MB, AH, and EB). In Fig. 5 a correlation was attempted between the percentage of normal metaphases and that of proerythroblasts, erythroblasts plus myelocytes, and mature granulocytes. Again, there was no apparent correlation. Unexpectedly, clusters were found to be present in the upper left and lower right areas of the figure. The former cluster consists

Fig. 3. The per cent of normal metaphases in the bone marrow plotted against survival time. (*AN-patients and xAA-patients.) Note that the patients on the baseline had no normal metaphases in the marrow and that the majority of examinations was performed within 1 mo of death.
Fig. 4. Per cent of abnormal metaphases plotted against that of myeloblasts plus promyelocytes in the marrow of A-patients. The points with patients' initials constitute the clusters discussed in the text of the paper.

Fig. 5. Per cent of normal metaphases plotted against that of proerythroblasts, erythroblasts, myelocytes, and maturer granulocytes in the marrow of A-patients. The points with patients' initials constitute the clusters discussed in the text of the paper.

primarily of cases in which abnormalities developed later in the disease. The latter cluster consisted of erythroleukemia cases. When these clusters are disregarded, however, a positive correlation appears to exist between the normal metaphases and the cellular elements presented.

Average figures for the bone marrow contents and life spans are given for the various patient groups in Table 4. Besides a difference in the life spans among the groups studied, there was also a difference in the cell differential counts of the bone marrow, even though such a difference in the latter cases to which a t-test was applied was not significant.

**DISCUSSION**

In the study presented, the initial cytogenetic examinations were performed, with but few exceptions, at the time of relapse of the AML or prior to therapy. Subsequent cytogenetic observations were performed at varying intervals and
Table 4. Some Clinical and Bone Marrow Data in Patients With Acute Myeloblastic Leukemia

<table>
<thead>
<tr>
<th>Patient Material</th>
<th>No. of Patients</th>
<th>Median Survival (± SE)</th>
<th>No. of Examinations</th>
<th>No. of Patients With Auer Bodies (10%)</th>
<th>Myeloblasts Plus Promyelocytes (32%)</th>
<th>Proerythroblasts Plus Erythroblasts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with chromosomal abnormalities (A-patients)</td>
<td>29</td>
<td>8.0 (6.7-9.5m)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with abnormal metaphases only (AA-patients)</td>
<td>10</td>
<td>3.2m (2.8-3.7m)</td>
<td>14</td>
<td>1</td>
<td>47.5±7.9</td>
<td>19.4±6.4</td>
</tr>
<tr>
<td>Patients with abnormal and normal metaphases (AN-patients)</td>
<td>19</td>
<td>10.3m (8.4-12.6m)</td>
<td>69</td>
<td>6</td>
<td>39.6±3.6</td>
<td>15.0±2.3</td>
</tr>
<tr>
<td>Patients without chromosomal abnormalities (N-patients)</td>
<td>40</td>
<td>11.5m (10.0-13.3m)</td>
<td>103</td>
<td>5</td>
<td>29.9±2.9</td>
<td>21.3±1.9</td>
</tr>
</tbody>
</table>

*Standard error obtained by the use of Fig. 2.
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frequencies, largely depending on the survival time of the patients and/or their response to therapy. On the basis of these karyotypic analyses the patients were divided into those whose marrows were never shown to contain aneuploid metaphase (N-patients), and those patients who at one time or another had aneuploid cells in their marrows (A-patients). The latter group was further subdivided into those patients whose marrow contained at least one normal metaphase during the course of the disease (AN-patients) and those patients whose marrow contained exclusively aneuploid cells (AA-patients).

Before some of the specific aspects of the study presented are discussed, we would like to stress what appear to us to be the salient features of and deductions from the results of this paper. In our opinion, the detection of even one normal metaphase during the initial (prior to treatment) marrow examination in A-patients is a terribly important finding, particularly regarding the prognosis and response of the patient to therapy. In all probability the presence of normal metaphases indicates that the patient is capable of repopulating his marrow with normal cellular elements in association with the response of the AML to therapy. On the other hand, AA-patients, who do not have any normal metaphases in their marrow, have a very unfavorable prognosis and their poor clinical course may be related to the absence of normal, diploid cell precursors in the marrow. Hence, even though the leukemia may respond to therapy, the patient is in the unfortunate position of not having normal cellular precursors to repopulate his marrow with.

The situation with N-patients is complicated. Since the leukemic cells of these subjects with AML did not contain visibly recognizable chromosomal changes, except for the fuzzy and ill-defined appearance of the leukemic chromosomes in some cases, it is impossible, at present, to ascertain which diploid metaphases are of leukemic and which of normal cell origin. Thus, it is possible that in some N-patients the total metaphase population is of leukemic origin and these subjects with AML will not fare much better than the AA-patients. The application of new cytologic techniques, e.g., fluorescence, “banding” pattern staining, may possibly yield information which will allow differentiation of the leukemic diploid metaphases from those of nonleukemic cell origin. Only then will it be feasible to interpret the findings in N-patients, comparably to those in the A-group. Nevertheless, the longer life-span and milder manifestations of the N-patients indicate that in most of these cases the marrow metaphase population contained a significant number of those which originated from normal marrow cells. The presence of the latter appears to endow the patient with a much better prognosis.

Surprisingly, a single marrow sample from a single site, whether sternal or iliac, appears to represent faithfully the overall cyrogenetic situation of the marrow in patients with AML and the examination of 25 cells (or even less) supplies sufficient karyotypic information for analysis and evaluation. Furthermore, as shown in Fig. 3, the presence of any normal metaphases, rather than their percentage, is more crucial in reflecting and possibly determining the course of the AML, than afforded by other cyrogenetic and cytologic parameters.
In the present study, 42% of the AML patients had chromosomal abnormalities in the marrow cells (A-patients). The results are in accord with previous reports.\textsuperscript{1-4,12} It was of interest to determine whether these cytogenetically different patients belonged to a single or different clinical entities. Thus, a comparison of the clinical parameters among the various groups of patients could be of help in answering this question.

Serial cytogenetic examinations on the same patients revealed that the percentage of cells with chromosomal abnormalities in A-patients is generally high in relapse and low in remission, as has been reported by others (Fig. 4).\textsuperscript{1,2,5} But, there were several cases in which this rule did not hold true. There were three patients (EB, MB, and AH) in whom chromosomal abnormalities appeared for the first time in the later stages of the acute leukemia, one patient (JO) in whom initial karyotypic changes disappeared in the middle course of the disease and new abnormalities appeared in the later stages of the acute leukemia, and another patient (PN) in whom additional cytogenetic abnormalities appeared late in the disease. The fact that the former three patients were not in remission when the initial examinations were performed is clearly indicated by the appearance of clusters in the lower right part of Fig. 4 and at the upper left area of Fig. 5. These clusters indicate that the percentage of the leukemic cells was already high in the early stages of their disease, despite the absence of chromosomal abnormalities. These findings suggest that there is no essential difference in the leukemogenic progression between the patients with abnormalities (A-patients) and those without them (N-patients).

It should be noted that one AN-patient (RM), who had only abnormal metaphases on admission, 1 mo later was shown to have only normal metaphases, after treatment with thioguanine and cytosine arabinoside. This patient has continued to be in remission for about 20 mo while on maintenance doses of the drugs. This is the only exceptional patient among those with only abnormal metaphases in the initial stages and who responded very successfully to treatment. The mechanism of induction of the remission in this patient deserves careful evaluation.

Among the A-patients there was a small number of subjects (AA-patients), mostly elderly, in whom normal metaphases could never be detected in the marrow specimens, even upon repeated examinations. Even though there is a possibility that in some of these patients normal metaphases would have been found upon more frequent cytogenetic analyses and, thus, these cases would then belong to the group of AN-patients, the distinct possibility of the existence of a unique group (AA-patients) of patients with AML is likely from the fact that in only nine out of 69 examinations on AN-patients did the marrow lack normal metaphases and that in only two AN-patients with an initial solely aneuploid marrow did diploid cells appear thereafter.

Since there was a definite difference between the life spans of AA- and AN-patients, we propose that the AA-patients may constitute a group separate from the rest of the AML patients. We do not know, as yet, whether the AA-patients represent an essentially new clinical entity or constitute a subgroup of AML, which may be, for example, called fulminant AML, or
whether these subjects are merely in the terminal stages of AML. The fact that some AN-patients lack normal metaphases in the terminal stages of the leukemia, may indicate a possible relationship of the absence of normal metaphases and the presence of only abnormal karyotypes (as in the AA-patients) with the stage of AML. At least, such cytogenetic findings are important in that they indicate that AML patients with only abnormal metaphases in their marrow appear to have an extremely poor prognosis.

When the clinical parameters of A-patients and N-patients were compared, it was apparent that, generally, the N-patients had a somewhat milder clinical course than the former patients: the N-patients lived longer, had less myeloblasts and promyelocytes and more proerythroblasts and erythroblasts in their marrows and a lower incidence of Auer bodies. Even a comparison of the N-patients with the AN-patients only, revealed a tendency for the former group to have milder clinical features.

SUMMARY

The results presented indicate that the presence of normal (diploid) metaphases during the initial marrow examinations, i.e., before treatment or during frank relapse, of patients with AML and aneuploid leukemic cells in the marrow (AN-group) is a very important finding. The presence of any diploid metaphases in such aneuploid marrows endows the case with a relatively favorable prognosis. In contrast, the absence of any diploid metaphases, i.e., AA-patients with totally aneuploid metaphases in their marrow, is a very poor prognostic sign, for such patients tend to have a very short lifespan.

Among the 69 patients with acute myeloblastic leukemia (AML) whose bone marrow chromosomes were studied, 29 had abnormal metaphases at least once during their clinical course (A-patients), whereas 40 showed no abnormalities (N-patients). Among the former patients, ten cases were never associated with normal metaphases, even upon repeated examinations (AA-patients), and 19 others had more than one normal metaphase during their course (AN-patients). The majority of the bone marrows without normal metaphases were obtained within 1 mo of death. The median life spans were 8.0 and 11.5 mo for A-patients and N-patients, and in the former group, 3.2 and 10.3 mo for AA- and AN-patients, respectively.

The appearance of chromosome abnormalities in the later stages of the disease in three patients with AML and the involvement by cytogenetic changes of both the erythroid and myeloid cell systems in erythroleukemia, were amply supported by the cellular differential counts obtained on the same marrow material as that on which chromosomal analyses were performed.

The clinical data indicate that N-patients may constitute a subgroup of AML with milder manifestations, as compared with those of A- or AN-patients.

The importance of the presence of normal metaphases in the prognosis of AML and a possible correlation of AA-patients with erythroleukemia is indicated by the results presented. There is a distinct possibility that the AA-patients may constitute a unique subgroup of AML with a fulminant clinical course and very poor prognosis. It is hoped that similar analyses of cytogenetic
data by other investigators on additional groups of patients with AML will shed more light upon the concepts presented in this paper.

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REFERENCES

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