Prediction of Response to Chemotherapy in Acute Myelocytic Leukemia

By Harvey D. Preisler

Marrow specimens obtained from 23 patients with acute myelocytic leukemia were exposed to cytosine arabinoside and/or daunorubicin in vitro, and the effects of these agents on colony formation in vitro was determined. Thymidine suicide indices were determined as well, which permitted a distinction to be made between kinetic and metabolic resistance to cytosine arabinoside. The sensitivity of the colony-forming cells to the two chemotherapeutic agents did not correlate with each other, indicating that sensitivity to each was independently determined. The relationship between in vitro sensitivity to daunorubicin and cytosine arabinoside and response to 25 courses of in vivo therapy with these two agents administered to 21 patients was determined. These studies indicated a clear-cut relationship between in vitro drug sensitivity and in vivo response with patients whose leukemic cells were sensitive to both agents entering complete remission, whereas patients whose leukemic cells were insensitive to one or both drugs in vitro failed to enter remission.

Chemotherapeutic regimens currently used for treating acute nonlymphocytic leukemia always produce significant toxicity but do not always produce antileukemic effects. The nature of the disease and of the effects of drugs on the disease make it difficult, if not impossible, to clinically evaluate the therapeutic effects of a regimen before the entire course of therapy is administered. Thus, the toxicity of a course of therapy is guaranteed but benefit is not. Even when leukemic cell drug resistance is clinically recognized, the toxic effects of the chemotherapeutic agents that have already been administered are frequently so severe that a change in therapeutic regimen must be delayed until the toxic effects of the therapeutically ineffective regimen abate. Since the likelihood of a fatal event increases with the duration of pancytopenia, patients often do not survive long enough to permit a change in therapeutic regimens. The availability of in vitro methods capable of determining the sensitivity of leukemic cells to specific chemotherapeutic agents would greatly facilitate the treatment of this disease by providing a means for rationally selecting remission induction regimens appropriate for individual patients.

The studies reported here were designed to determine whether the effects of cytosine arabinoside (ara C) and daunorubicin (DNR) on the ability of leukemic cells to clone in vitro were correlated with the outcome of remission induction therapy using these two agents. These studies have demonstrated that patients whose clonogenic leukemic cells (LCFU-c) were sensitive to both drugs in vitro entered remission, while patients whose LCFU-c were resistant to either or both agents were remission induction failures.

Materials and Methods

Patients Studied

Bone marrow specimens were obtained from 23 patients with acute myelocytic leukemia. Of these, 20 patients received remission induction therapy consisting of daunorubicin (DNR) 45 mg/sqm/day on days 1, 2, and 3 and cytosine arabinoside (ara-C) 100 mg/sqm/day for 10 days administered by continuous intravenous infusion, and one patient (no. 23) was treated with DNR 45 mg/sqm/day on days 1, 2, and 3, ara-C 200 mg/sqm/day on days 1-5 and 6-thioguanine (6-TG) 200 mg/sqm po/day on days 1-5. Patient 6 initially was treated with DNR ara-C as described above, and upon relapse, was treated with DNR ara-C-6-TG as described above. Twenty-five courses of remission induction therapy were administered to these patients. The clinical characteristics of the patients are presented in Table I.

Criteria for Assessing the Sensitivity of Leukemia Cells to Therapy In Vivo With Ara-C–DNR and Analysis of Data

The criteria used to define complete remissions (CR) were those described by Ohnuma et al. Patients who failed to enter complete remission were divided into drug-resistant and inevaluable categories. The drug-resistant category includes those patients whose bone marrow was never rendered hypocellular by chemotherapy (type I failures) as well as those patients whose bone marrow was rendered hypocellular but in whom leukemic cells reappeared when the marrow regenerated (type II failures). The inevaluable category included patients who did not survive long enough to permit a conclusion to be reached as to whether or not they would enter remission or have persistent disease. This category includes those patients who died early during the course of chemotherapy as well as those who expired with a hypoplastic bone marrow. Both nonparametric (Mann-Whitney) and parametric (Student's t test) statistical tests were used to evaluate the relationship between in vitro drug sensitivity and the outcome of remission induction therapy.

Methods of Study

Five milliliters of bone marrow was aspirated into a syringe containing 1 ml of 4% sodium citrate. The erythrocytes were lysed.

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Concentration of 0.3 or 3 μg/ml. After 1 hr of incubation, the cells appropriate amount of ara-C was added to make a final drug atmosphere consisting of 5% CO₂ 95% air. At the end of 1 hr, an complete medium (RPMI 1640 made 10% with fetal calf serum) as bated at 5 × 10⁶ cells/ml in complete media at 37°C in a humidified clonogenic leukemic cells that were in S phase during the 1-hr activity 3H-TdR was used as a measure of the proportion of TdR (55 Ci/mmole, 0.5 mCi/ml) was substituted for ara-C.3

Exposure to Daunorubicin (DNR)

Exposure to Cytoinosine Arabinoside (ara-C)

Cells from leukemic marrow or peripheral blood were preincubated at 5 × 10⁶ cells/ml in complete media at 37°C in a humidified atmosphere consisting of 5% CO₂ and 95% air at 37°C. After 7 days, the plates were fixed with 3% glutaraldehyde and the number of cluster-colonies (≥ 4 cells/group) in triplicate plates counted by a single observer. This individual did not know the identity of the plates that were being counted since the plates were coded by a different individual according to a computer-generated random number sequence. The latter individual also decoded the experiment once counting was complete. In each study more than 50 cluster-colonies were present in the control plates, and the standard error of the mean was less than ± 10%.

Table 1. Characteristics of Patients who Were Studied

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Sex</th>
<th>Age</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>♀</td>
<td>28</td>
<td>AML Previously untreated</td>
</tr>
<tr>
<td>2</td>
<td>♀</td>
<td>72</td>
<td>AML Previously untreated</td>
</tr>
<tr>
<td>3</td>
<td>δ</td>
<td>48</td>
<td>AMMol Previously untreated</td>
</tr>
<tr>
<td>4</td>
<td>δ</td>
<td>12</td>
<td>AML Previously untreated</td>
</tr>
<tr>
<td>5</td>
<td>δ</td>
<td>57</td>
<td>AML Previously untreated</td>
</tr>
<tr>
<td>6</td>
<td>δ</td>
<td>68</td>
<td>AML Previously untreated</td>
</tr>
<tr>
<td>7</td>
<td>δ</td>
<td>69</td>
<td>AML Previously untreated</td>
</tr>
<tr>
<td>8</td>
<td>δ</td>
<td>24</td>
<td>AMMol Previously untreated</td>
</tr>
<tr>
<td>9</td>
<td>♀</td>
<td>30</td>
<td>AML Previously untreated</td>
</tr>
<tr>
<td>10</td>
<td>♀</td>
<td>37</td>
<td>AEL Resistant to ara-C + DNR</td>
</tr>
<tr>
<td>11</td>
<td>♀</td>
<td>62</td>
<td>AML Relapsed AML</td>
</tr>
<tr>
<td>12</td>
<td>♀</td>
<td>43</td>
<td>AML Previously untreated</td>
</tr>
<tr>
<td>13</td>
<td>δ</td>
<td>19</td>
<td>AEL Previously untreated</td>
</tr>
<tr>
<td>14</td>
<td>♀</td>
<td>53</td>
<td>AEL Previously treated for Hodgkin's disease with radiation therapy and alkylating agents</td>
</tr>
<tr>
<td>15</td>
<td>♀</td>
<td>63</td>
<td>AMMol Relapsed AML</td>
</tr>
<tr>
<td>16</td>
<td>δ</td>
<td>56</td>
<td>AML Previously untreated</td>
</tr>
<tr>
<td>17</td>
<td>δ</td>
<td>53</td>
<td>AML Previously untreated</td>
</tr>
<tr>
<td>18</td>
<td>♀</td>
<td>48</td>
<td>AML Previously untreated. History of myelofibrosis.</td>
</tr>
<tr>
<td>19</td>
<td>♀</td>
<td>63</td>
<td>AML History of multiple myeloma previously treated with alkylating agents.</td>
</tr>
<tr>
<td>20</td>
<td>♀</td>
<td>52</td>
<td>AML Previously untreated</td>
</tr>
<tr>
<td>21</td>
<td>♀</td>
<td>72</td>
<td>AML Relapsed AML</td>
</tr>
<tr>
<td>22</td>
<td>δ</td>
<td>57</td>
<td>AMMol Previously untreated</td>
</tr>
<tr>
<td>23</td>
<td>δ</td>
<td>14</td>
<td>AMOL Relapsed AMOL</td>
</tr>
</tbody>
</table>

AML, acute myelocytic leukemia; AMMol, acute myelomonocytic leukemia; AMOL, acute monocytic leukemia; AEL, acute erythroleukemia.

Cloning in Agar

After incubation, cells were diluted to 10⁶ cells/ml of complete media. One-tenth milliliter of this cell suspension was mixed with 0.75 ml of 0.3% agar and plated over a 2.5-ml layer underlay of 0.5% agar made 20% with colony-stimulating factor. The cultures were incubated in a humidified atmosphere consisting of 5% CO₂ and 95% air at 37°C. After 7 days, the plates were fixed with 3% glutaraldehyde and the number of cluster-colonies (≥ 4 cells/group) in triplicate plates counted by a single observer. This individual did not know the identity of the plates that were being counted since the plates were coded by a different individual according to a computer-generated random number sequence. The latter individual also decoded the experiment once counting was complete. In each study more than 50 cluster-colonies were present in the control plates, and the standard error of the mean was less than ± 10%.

RESULTS

Table 1 provides the clinical data for the patients who were studied. The group is heterogeneous with respect to age, diagnosis, and treatment history. All patients save 8c, 18, and 19 received remission induction therapy subsequent to the laboratory studies. Patient 6 was studied, treated, and entered remission. He relapsed 4 mo later, was restudied, and retreated as described in Materials and Methods. Twenty-five courses of therapy were administered resulting in 10 complete remissions, 10 instances of documented resistant disease (type I or II failures). 4 patients expired subsequent to chemotherapy during a period of severe marrow hypoplasia (type IV failures), and one patient expired on day 2 of therapy. Patients 18 and 19 declined to receive therapy and patient 8c was deemed to be resistant to therapy since his disease recurred immediately after a course of intensive consolidation therapy with ara-C and an anthraclycline antibiotic. He has subsequently received an allogeneic bone marrow transplant.

Characteristics of the In Vitro Assays

The sensitivity of the leukemic CFU-c (LCFU-c) to ara-C varied among the patients studied (Table 2). In seven instances, exposure to low concentrations of ara-C resulted in an increase in the number of cluster-colonies produced. This was not seen with DNR. In 13 of the 22 trials in which leukemic cells were exposed to more than a single concentration of ara-C, the proportion of CFU-c killed by the high and low concentrations of the drug were indistinguishable, while for 9 patients the higher drug concentration killed substantially more CFU-c than the lower concentration. Since the differences in in vitro concentrations were ten-fold, these observations suggest that for at least some patients, increasing the in vivo concentration of ara-C above a minimal level (0.3 μg/ml) would not increase therapeutic efficacy, while for other patients such an
increase would render leukemic CFU-c more responsive to chemotherapy.

Tritiated thymidine killed between 0% and 100% of the CFU-c of the different patients. These data can also be found in Table 2. There was no general correlation between the percent CFU-c killed by ara-C and that killed by \(^3\)H-TdR. Table 2 also reports the effects of DNR on the leukemic CFU-c of 19 patients. At the 0.1 \(\mu\)g/ml concentration, there were significant differences in the sensitivity of the CFU-c of the various patients to DNR, while at the higher concentration, such differences were not detectable since virtually all CFU-c were killed. There was no correlation between the CFU-c sensitivity to 0.3 or 3 \(\mu\)g/ml of ara-C and to 0.1 \(\mu\)g/ml of DNR \((r = 0.539 \text{ and } 0.578, \text{ respectively})\). The effect of simultaneous exposure to ara-C and DNR appeared to be no more than additive for 14 patients, but possibly synergistic for patients 18 and 21.

Patients 1, 8c, and 14 were studied on two occasions several days to 1 wk apart during a period of stable disease. The reproducibility of the in vitro assay methods was demonstrated by the fact that the percent CFU-c killed by ara-C, the \(^3\)H-TdR suicide index, and the percent CFU-c in S phase that were killed by ara-C were indistinguishable on the two separate occasions that the studies were carried out (Table 2).

**Relationship Between In Vitro Drug Sensitivity and In Vivo Response to Therapy** (Table 2, Fig. 1a and b)

Table 2 lists the treatment outcome of 25 courses of remission induction therapy together with the sensitivity to ara-C and DNR of the LCFU-c of the patients.
being treated, and Fig. 1 presents the treatment outcome on the basis of each test. The proportion of LCFU-c killed by 0.3 \( \mu g/ml \) of ara-C ranged from 0%–60% for drug-sensitive patients with \( \geq 30\% \) killing for 5 of the 7 specimens. The range of killing for drug-resistant patients ranged from 0%–51% with \( \leq 13\% \) killing for 7 of 8 drug-resistant specimens. The mean \( \pm \) SE for percent LCFU-c killed for the drug-sensitive and drug-resistant patients were 30% \( \pm \) 9% and 9% \( \pm \) 6%, respectively. The \( p \) value for these differences are 0.08 for a Mann-Whitney test and 0.05 for a Student’s \( t \) test. The proportion of LCFU-c killed by 3 \( \mu g/ml \) ara-C ranged from 0% to 64% with \( \geq 23\% \) LCFU-c being killed in 7 of the 9 specimens obtained from patients who entered CR. For patients who failed to enter remission because of drug-resistant disease, the percent LCFU-c killed ranged from 0% to 53% with \( \geq 25\% \) of the CFU-c killed in 7 of the 8 specimens. The mean \( \pm \) SE of percent LCFU-c killed by ara-C for the CR patients and resistant patients were 34% \( \pm \) 8% and 18% \( \pm \) 6%, respectively. The \( p \) value for these differences are 0.05 for both a Mann-Whitney test and a Student’s \( t \) test.

The \( ^3\)H-TdR suicide index varied from 0% to 96% with a mean \( \pm \) SE of 43% \( \pm \) 7%. There was no direct relationship between SI and response to therapy. The percent of LCFU-c that were in S phase during exposure to ara-C and were killed by ara-C can be found in Table 2, column 7. Values ranged from 0% to 440%, with a mean \( \pm \) SE of 79% \( \pm \) 28%. Considering the patients who entered CR values ranged from 0% to 440% with a mean \( \pm \) SE of 105% \( \pm \) 44% as compared to a range of 0%–200% with a mean \( \pm \) SE of 50 \( \pm \) 33% for patients with resistant disease. The difference in percent S phase LCFU-c killed by ara-C for drug-sensitive and drug-resistant patients was significant at a \( p \) value of 0.0466 (Mann-Whitney test). Note that a value of ara-C/SI > 1 indicates that ara-C killed more CFU-c than did \( ^3\)H-TdR.

The differences in LCFU-c sensitivity to 0.1 \( \mu g/ml \) DNR between patients with drug-resistant disease and patients who entered CR were highly significant. For the 7 patients who entered remission, the percent CFU-c killed varied from 0% to 76%, while for patients with resistant disease, the range was 8%–33%. The mean \( \pm \) SE percent CFU-c killed in the former group of patients was 44% \( \pm \) 8%, while the comparable figure for patients with drug-resistant disease was 22% \( \pm \) 4%. The \( p \) value for these differences using a Mann-Whitney test was 0.01, and for a \( t \) test, 0.025.

The sensitivity of the LCFU-c of 13 patients to both ara-C and DNR (exposure to each drug separately) were determined. Eight of the 13 patients entered CR and the sensitivity of the LCFU-c of these patients to ara-C (ara-C/SI) all exceeded 0.71, and the percent CFU-c killed by DNR in each case exceeded 34% except for patient 21. In her case, the LCFU-c were apparently resistant to each agent alone but were sensitive to the two agents in combination. By contrast, the LCFU-c of the 5 patients who failed to enter CR were either sensitive to ara-C but insensitive to DNR (patient 12), sensitive to DNR but not ara-C (patients 8c, 13), or insensitive to both (patients 8a, 9a). The LCFU-c of 14 patients were simultaneously exposed to ara-C and DNR. Nine patients entered CR with the percent LCFU-c killed being \( \geq 46\% \) in 8 of the 9 patients (\( \bar{X} \pm SE = 49\% \pm 7\% \)). For the 5
patients with resistant disease, the percent LCFU-c killed varied from 0% to 21%, with a mean of 8% ± 4%. These differences are significant at 0.008 and 0.0005 level for Mann-Whitney and Student's t test analyses, even though the "0" for patient 6a was probably a laboratory error since each ara-C and DNR alone produced significant killing of LCFU-c.

Four patients expired with severely hypoplastic bone marrows (type IV failure), indicating that the majority of their leukemic cells were sensitive to at least one of the two drugs administered in vivo. The LCFU-c of 3 of the 4 patients were significantly sensitive to ara-C. Bone marrow specimens of 3 patients were tested only for ara-C sensitivity. One patient (14) had ara-C-sensitive LCFU-c and died hypoplastic. The LCFU-c of a second patient (9b) demonstrated resistance to ara-C but the patient entered CR (sensitivity to DNR was not measured), while the LCFU-c of the third patient (14) were sensitive to ara-C, and this patient died.

**DISCUSSION**

The studies reported here demonstrate a significant correlation between the sensitivity in vitro of LCFU-c to ara-C and DNR and the ability of a remission induction regimen composed of these drugs to induce a complete hematologic remission. When considered alone, the killing of LCFU-c by DNR was more highly correlated with treatment outcome than was the effect of ara-C on LCFU-c, perhaps reflecting the relative contribution of each drug to the efficacy of the remission induction regimen. Patients whose LCFU-c were sensitive to both drugs entered CR, while patients whose LCFU-c were sensitive to one drug and not to the other did not enter remission. It is likely, however, that as our sample size increases, patients whose leukemic cells are very sensitive to one drug and not to the other and who enter remission will be found, since each drug administered alone at the doses used in our combination regimen will induce a complete remission in a low percentage of patients.

There are at least two possible explanations why our studies have been successful while the attempts of other investigators to predict remission induction outcome on the basis of in vitro drug sensitivity assays have been unsuccessful. The assays employed by other investigators, such as measurement of drug activation and metabolism or measurement of the effects of drugs on DNA synthesis, did not measure the ability of the drug to kill the leukemic cells since activation of a drug does not guarantee the presence of a critical drug-sensitive pathway and inhibition of DNA synthesis is not necessarily lethal. By contrast, the assays used in the studies reported in this article measured cell death. Secondly, other investigators measured drug effects on the leukemic cell population as a whole, whereas our studies were directed towards the clonogenic subpopulation. Previous studies from this laboratory have demonstrated that the cell cycle characteristics and the sensitivity to ara-C of the leukemic cell population as a whole was not necessarily reflective of that of the clonogenic cells.

Figure 1 (A and B) provides data regarding the relationship between ara-C sensitivity and treatment outcome for 21 patients. Inspection of the figure demonstrates that when dealing with extremes of cell kill, it is not difficult to distinguish between patients with ara-C-sensitive and ara-C-resistant LCFU-c. However, there appears to be an overlap in the area of 17%–25% cell kill. Estimating LCFU-c sensitivity on the basis of the percentage of S phase CFU-c killed by ara-C permits a distinction to be made between ara-C-sensitive and resistant LCFU-c. For example, the LCFU-c of patients 6, 8c, 10, 15, and 19 all appear to have similar sensitivity to ara-C (23%, 25%, 18%, 21%, 17% killed, respectively); however, when the percent of CFU-c in S phase that were killed by ara-C is calculated, it is clear that the LCFU-c of patient 6 were much more sensitive than the others and, in fact, were equally as sensitive as the CFU-c of patient 8b (ara-C/SI, 0.79 and 0.80, respectively) even though on the basis of absolute LCFU-c kill, the ara-C sensitivity of the LCFU-c of these two patients appeared to be quite different. This analytical approach is based on the fact that only cells synthesizing DNA during exposure to ara-C will be killed by the drug. Given this fact, it is clear that when measuring the effects of any S-phase-specific drug on a cell population, quantitation of the proportion of cells in the appropriate phase of the cell cycle is essential, since low cell kill could result either from innate "metabolic resistance" (for ara-C, for example, low kinase or high deaminase levels) or if few cells were in S phase during exposure to the drug (kinetic resistance). This distinction is of critical importance when a short drug exposure in vitro assay is used to predict the effects of much longer term drug exposure in vivo, since even if the absolute number of LCFU-c killed by a 1-hr exposure in vitro were low but if most or all of the S phase cells were killed (patient 6), then a continuous infusion of the drug in vivo (10-day infusion of ara-C, for example) would be clinically effective. By contrast, if many LCFU-c were in S phase during the 1-hr exposure to ara-C in vitro, but few were killed, then this would be evidence of metabolic resistance and it would be unlikely that ara-C would be effective in vivo (patients 10, 11, 13, 15, 17, 18, 19).

Measurement of ara-C/SI permitted two observa-
tions that would otherwise have not been possible. Prior to receiving his first course of chemotherapy, the LCFU-c of patient 8 were resistant to ara-C (0 cell kill), very insensitive to DNR (17% cell kill), and very few, if any, LCFU-c were in cycle (0 SI). Administration of a course of remission induction therapy resulted in a decrease in marrow cellularity from 4+ to 1-2+ with persistence of leukemia. Studies carried out immediately before administration of a second course of chemotherapy demonstrated that the LCFU-c were now actively dividing (70% SI) and were highly sensitive to both ara-C and DNR. The patient entered CR after this second course of therapy. It appears that his LCFU-c were initially insensitive to ara-C on a cell cycle kinetic basis and that reduction of leukemic cell numbers in vivo by the first course of therapy recruited the LCFU-c into cycle permitting them to manifest their sensitivity to ara-C. Unfortunately, this patient has subsequently relapsed and measurement of the sensitivity of his LCFU-c now demonstrated metabolic resistance to ara-C and reduced sensitivity to DNR (8c, Table 2). Similarly, the LCFU-c of patient 6 were drug sensitive prior to successful remission induction therapy and were drug resistant both in vitro and in vivo when the patient relapsed.

The second observation made possible by determining the ara-C/SI is that in several patients (2, 12, 20), ara-C killed many more LCFU-c than could be accounted for by the percent CFU-c in S phase. We have never seen this in our studies of normal CFU-c where ara-C invariably killed fewer CFU-c than did 3H-TdR. It is possible that this observation may account in part for the therapeutic efficacy of this drug. The mechanism for greater than expected killing by ara-C may be related to prolonged retention of ara-C by these cells so that effective exposure to ara-C exceeded the 1-hr incubation period.

Evaluation of the relationship between ara-C-DNR sensitivity and the response to antileukemia therapy strictly on the basis of whether or not a patient enters remission may be too restrictive. Patients with drug-sensitive disease may fail to enter remission as a result of death due to intercurrent disease. Since an in vitro drug sensitivity assay can hardly be expected to predict death due to infection, we excluded from analysis those patients who expired before a determination could be made as to whether or not the patients were going to enter remission. This applied to 5 patients in this study, 4 of whom were type IV failures and 1 who died on day 2 of therapy. By definition, the majority of leukemic cells of patients who are type IV failures were drug sensitive, since these patients expired during a period of severe marrow hypoplasia. The leukemic cells of 3 of these patients were very drug sensitive in vitro, but those of one patient (17) were drug resistant in vitro. Whether any or all of these patients would have entered remission is not known.

The studies reported here have demonstrated a high degree of correlation between in vitro drug sensitivity to ara-C and DNR and response to remission induction therapy with these two agents. While the precise levels of drug sensitivity that can differentiate between drug-sensitive and drug-resistant disease will require the study of many more patients than reported here, the existence of a relationship between in vitro sensitivity and in vivo response is clear-cut. The most sensitive test for recognizing leukemia sensitive or resistant to therapy with ara-C-DNR has been exposure of leukemic cells to ara-C and DNR simultaneously. Nevertheless, we continue to expose LCFU-c to each drug separately so that we can recognize the sensitivity of the LCFU-c to each agent so that chemotherapy regimens can be specifically designed for individual patients.

Finally, it should be remembered that drug sensitivity is only one factor in determining whether or not a patient will enter remission. The outcome of remission induction therapy is equally dependent on a patient's biologic characteristics, since these play a major role in determining whether a patient can survive remission induction therapy. Therefore, the ability to predict the outcome of remission induction therapy will ultimately depend on multivariate analyses that will take into account the clinical prognostic parameters together with the drug sensitivity of the leukemic cells.

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REFERENCES


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