Causes of Initial Remission Induction Failure in Acute Myelogenous Leukemia


One-hundred and sixty-one of 378 previously untreated patients with acute myelogenous leukemia (AML) failed to enter complete remission with a combination of anthracycline, cytosine arabinoside, vincristine, and prednisone between 1973 and 1979. Thirty-six of the failing patients (22%) were considered chemotherapy failures. As in the past, the remainder failed largely because of death from infection. However, despite the routine use of prophylactic platelet transfusions, hemorrhage was a major cause of death in 33%. Thirty-seven percent of the fatal infections were due to fungi and the incidence of fungal infection was as high during the second week of treatment as later. Age >50 yr predisposed to fatal infection but not chemotherapy failure, while the presence of an antecedent hematologic disorder increased the risk of both fatal fungal infection and resistance to chemotherapy. Patients with an initial white blood cell count of >25,000/μl were more likely to die of hemorrhage at all times during treatment. Improvement in supportive care remains crucial if improved complete rates are to be forthcoming in previously untreated patients.

Despite improvement in complete remission rates, a considerable number of patients with acute myelogenous leukemia (AML) still fail to achieve complete remission (CR) with initial remission induction treatment. It has been widely recognized that most failures are due to death during induction from infection and hemorrhage. With recent advances in chemotherapy and supportive care, it is again important to estimate how many initial induction failures result from inherent resistance to chemotherapy and how many result from fatal infection and/or hemorrhage before chemotherapy can achieve CR.

Determination if pretreatment characteristics can identify patients at increased risk of a given fatal complication or of having refractory disease would allow alternate chemotherapeutic regimen to be given to those likely to be resistant to standard treatment and different approaches to supportive care to be explored in those patients most likely to benefit from them. Furthermore, if specific periods of high risk could be identified, optimal supportive care would be given at the most appropriate time.

This study reports the causes of initial remission induction failure in a large number of adults with previously untreated AML treated with current chemotherapy. It was undertaken to develop specific treatment strategies for patients who have a high probability of dying from particular complications.

MATERIALS AND METHODS

Two-hundred and seventy-three previously untreated adult patients with AML, including acute myeloblastic leukemia (AML), acute myelomonocytic leukemia (AMML), acute monocytic leukemia (AMoL), acute promyelocytic leukemia (APL), and erythroleukemia (EL), received remission induction therapy with cytosine arabinoside, vincristine, and prednisone combined with adriamycin (ADOAP) between 1973 and 1979. An additional 105 patients aged 50 or over received rubidazone combined with the other three drugs between 1976 and 1979 (ROAP). Thus, a total of 378 patients with previously untreated AML received chemotherapy between 1973 and 1979. Patients with blastic transformation of chronic myelogenous leukemia were excluded from this analysis. Patients under age 50 were treated in laminar air-flow rooms if available. Some patients received prophylactic systemic antibiotics outside the laminar air-flow rooms as part of a study comparing the efficacy of laminar air-flow rooms, prophylactic systemic antibiotics, and no prophylaxis in preventing infectious morbidity and mortality during remission induction. No patients were excluded from remission induction chemotherapy because of age, prior history of/or treatment for a previous malignancy, or presence of an antecedent hematologic disorder (AHD), defined as a documented abnormality in the peripheral blood of at least 1-mo duration prior to diagnosis or treatment. Patients with platelet counts less than 20,000/μl were given prophylactic platelet transfusions. Patients presenting with white blood cell counts above 50,000/μl were leukapheresed but not given hydroxyurea.

The causes of failure are defined below.

Infection

Bacterial sepsis. A clinical picture of infection and a positive blood culture during the last 7 days of life or at postmortem examination. Common contaminants such as Staphylococcus epidermidis, Bacillus sp., and Corynebacter sp. were disregarded unless grown from two or more specimens of blood.

Fungal sepsis. Histologic evidence of tissue (other than lung alone) invasion by fungi, or a positive antemortem blood culture for Candida sp., combined with a compatible clinical course.

Bacterial pneumonia. Extensive pneumonia at autopsy or on the last premortem chest x-ray in patients without autopsies. Bacteria had to be seen in or grown from lung tissue in autopsied patients, or grown as the predominant organism in two separate sputum cultures, one of which was taken during the last week of life in...
nonautopsied patients or grown from blood in both groups of patients.

**Fungal pneumonia.** Extensive lung tissue invasion by fungi or extensive pneumonia accompanied by a positive blood culture for *Canadida sp.* Sputum cultures for fungi were disregarded.

**Pneumonia organism unknown.** Extensive pneumonia, either at autopsy or on the last pre-mortem chest x-ray, without identification of the responsible pathogen as previously defined.

**Hemorrhage**

Hemorrhage was a cause of failure if it occurred in a vital organ and was described at autopsy as extensive. In nonautopsied patients: CNS hemorrhage—a decrease in the level of consciousness not explained by other factors; pulmonary hemorrhage—massive hemoptysis accompanied by acute respiratory failure; GI hemorrhage—massive melena or hematemeses accompanied by fall in blood pressure. The causes of hemorrhage follow:

- **Severe thrombocytopenia.** Less than 20,000 platelets/μl at or about the time of hemorrhage.
- **Disseminated intravascular coagulation (DIC).** Increased fibrin split products, or a thrombin time ≥3 sec longer than the control, or a decreased fibrinogen accompanied by an abnormal prothrombin time (PT) or partial thromboplastin time (PTT), or thrombi seen in multiple organs in association with a decreased fibrinogen or lengthened PT or PTT at or about the time of hemorrhage.
- **Possible DIC.** Abnormalities in PT, PTT, or fibrinogen not meeting the above definition.

**Organ Failure**

Severe impairment in the function of a vital organ not explained by hemorrhage or infection.

**Chemotherapy Failure**

Patients not in complete remission (as previously defined) after four courses of treatment were considered chemotherapy failures. Also included in this group were patients who achieved only partial remission (PR: same as CR but with 6–25% myeloblasts in the marrow); patients in whom treatment was changed before the fourth course because their physicians felt they had shown insufficient response to ADOAP or ROAP (less than 50% reduction in marrow leukemic infiltrate as defined below at the end of a course), and patients who achieved normal bone marrow differentials but in whom peripheral blood counts did not return to normal and who received no further chemotherapy.

The weekly mortality rate from a given complication was obtained by dividing the number of fatalities due to that complication during a particular week by the total number of patients at risk.

To assess response to antileukemia treatment, patients were categorized into those in whom the marrow leukemic infiltrate (MLI) (defined as percent myeloblasts plus promyelocytes in the bone marrow differential times percent cellularity on clot section) remained above 20% (group I) and those in whom the MLI was reduced to less than 20% (group II). Patients without autopsies were evaluable for antileukemic response if bone marrow examinations had been performed within the week prior to death. Patients in group II were subclassified as follows:

- **2A. Hypoplasia at death**—the MLI was below 20% at death
- **2B. Regrowth of leukemia**—leukemic cells repopulated the marrow so that the MLI exceeded 50% on one occasion or 20% on two consecutive occasions
- **2C. Complete remission**—as previously defined
- **2D. Partial remission**—as previously defined

### RESULTS

One-hundred and sixty-one of 378 total patients (43%) failed to achieve CR. Table 1 shows some characteristics of both the total patient population and of those patients who failed to achieve remission. As previously reported, patients who failed to achieve CR were more likely to have been older, to have had an antecedent hematologic disorder, and as a consequence, to have been treated with ROAP outside the protective environment. Failure rates were the same regardless of morphological diagnosis.

The outcome of treatment for each course can be seen in Table 2. The fraction of patients achieving CR with each course was relatively constant for courses 1 through 4. Four of the 19 patients (21%) who received a fourth course after failing the initial 3 courses achieved CR on the fourth course. None of the 8 patients who received a fifth or subsequent course obtained a CR. Therefore, the 13 patients not in CR by the end of 4 courses were considered chemotherapy failures. Twenty-three additional patients were considered chemotherapy failures because of treatment changes before course 4 (20 patients), or failure to

| Table 1. Characteristics of Total Patient Population Compared to Failing Patients |
|---------------------------------|---------------------------------|-------------------|
| **Total No. of Patients**       | **No. of Failed Patients (%)** |
| Age < 50 yr                     | 180                            | 55 (31)           |
| Age ≥ 50 yr                     | 198                            | 106 (54)          |
| No antecedent hematologic disorder | 290               | 98 (34)           |
| Antecedent hematologic disorder | 88                             | 63 (72)           |
| AML/AMML                        | 267/75                        | 116/29 (43/39)    |
| APL, AMOL, EL                   | 36                             | 16 (44)           |
| ADOAP/ROAP                      | 273/105                       | 105/56 (38/53)    |

**2E. Questionable regrowth of leukemia**—the MLI on one occasion was 20%–50%.

Statistical comparison between various groups was done using the Yates modification of the Chi-square test.

### Table 2. Outcome of Treatment in Patients With AML Undergoing Remission Induction

<table>
<thead>
<tr>
<th>Course No.</th>
<th>Total No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 No. (%)</td>
<td>202</td>
</tr>
<tr>
<td>2 No. (%)</td>
<td>62</td>
</tr>
<tr>
<td>3 No. (%)</td>
<td>19</td>
</tr>
<tr>
<td>4 No. (%)</td>
<td>19</td>
</tr>
<tr>
<td>Total</td>
<td>378</td>
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<table>
<thead>
<tr>
<th>Total entering</th>
<th>CR</th>
<th>Died</th>
<th>Change Rx</th>
<th>Off Rx</th>
<th>Further</th>
</tr>
</thead>
<tbody>
<tr>
<td>378</td>
<td>108 (29)</td>
<td>63 (17)</td>
<td>3 (1)</td>
<td>2 (1)</td>
<td>202 (53)</td>
</tr>
<tr>
<td></td>
<td>85 (42)</td>
<td>50 (26)</td>
<td>1 (1)</td>
<td>2 (1)</td>
<td>62 (31)</td>
</tr>
<tr>
<td></td>
<td>20 (32)</td>
<td>8 (13)</td>
<td>14 (23)</td>
<td>1 (2)</td>
<td>19 (31)</td>
</tr>
<tr>
<td></td>
<td>4 (21)</td>
<td>2 (11)</td>
<td>5 (26)</td>
<td>0 (0)</td>
<td>8 (42)</td>
</tr>
<tr>
<td></td>
<td>217 (57)</td>
<td>123 (33)</td>
<td>25 (7)</td>
<td>5 (1)</td>
<td>8 (2)</td>
</tr>
</tbody>
</table>
complete the study because of persistent pancytopenia (3 patients). Overall, 36 patients (9% of all patients treated, and 22% of all failing patients) were chemotherapy failures. In addition, 2 patients were lost to follow-up.

One-hundred and twenty-three patients died during the initial four courses (33% of all patients and 76% of all failures). The rate of death was highest during the second course (25%) and declined subsequently, so that only 13% and 11% of those receiving third and fourth courses, respectively, died during those courses. Of the 123 patients who died during the initial 4 courses, 113 (92%) died during the first 2 courses.

Deaths During Remission Induction

The causes of death in the 123 patients who died during the first 4 courses of chemotherapy are shown in Table 3. Eighty (65%) of these patients had postmortem examinations. Infection, either alone or in combination with hemorrhage and/or organ failure, accounted for most of the deaths. Hemorrhage was a contributing cause of death in a significant minority of patients, usually occurring together with infection. Organ failure was a relatively infrequent cause of death.

Twenty-seven percent of the fatal infections were septicemias alone, 26% were pneumonias alone, and 47% were combinations of septicemia and pneumonia. Therefore, 73% of all the fatal infections were septicemias, while pneumonia occurred in a similar percent.

Although bacteria were the most frequent pathogens, fungi, either alone or together with bacteria, were responsible for 37% of all fatal infections, 42% in autopsied patients, and 21% in nonautopsied patients. In 61% of the cases of pneumonia without positive blood cultures, no pathogen was recovered, and even in those cases in which an autopsy was performed, no organism was identified in 47% of these infections. No cases of fatal viral or protozoal infection were identified.

Gram-negative bacilli were responsible, either alone or in combination with gram-positive organisms, for 87% of the fatal bacterial infections. The corresponding figure for gram-positive organisms was 27%. Klebsiella sp. and Pseudomonas sp. were the most frequent gram-negative pathogens associated with fatal bacterial infection, and Enterococcus was the most frequent gram-positive pathogen responsible for death. A large majority of fungal infections were due to Candida sp. Although no cases of disseminated aspergillus were encountered, this organism was the most frequent cause of fatal fungal pneumonia.

Thirty-three of 41 patients with fatal hemorrhages (80%) had single sites of major bleeding. Six patients had 2, and 2 patients had 3 organs involved by hemorrhage. Overall, the most frequent sites were brain (22 patients), lungs (16 patients), and gastrointestinal tract (12 patients). There was an association between fatal pulmonary hemorrhage and fatal pneumonia. Although only 3 of 313 patients who did not die of pneumonia had fatal pulmonary hemorrhage, 12 of the 65 patients who died with pneumonia also had associated major pulmonary hemorrhage (p < 0.01).

Severe thrombocytopenia alone was the cause of hemorrhage in 14 of the 41 patients (34%). Five patients (12%) had DIC. Nineteen patients (46%) had both severe thrombocytopenia and coagulation abnormalities (DIC in 14, possible DIC in 5). In only 2 patients (5%), both with cerebral hemorrhage, was leukostasis a likely cause of death. Both these patients had abnormal coagulation and one had severe thrombocytopenia. In one patient (2%), the cause of hemorrhage was uncertain. A platelet count of ≤20,000/µL at or about the time of hemorrhage occurred in 34 of the patients (83%) and was equally as frequent among patients dying of CNS, pulmonary, or gastrointestinal hemorrhage. DIC or possible DIC was a proximate cause in 26 patients (63%) and was especially common in pulmonary hemorrhage: almost 90% of those with fatal pulmonary bleeding had coagulation abnormalities. DIC or possible DIC was related to major infection in 18 of the 26 patients (69%) and to leukemia in 8 patients (31%). Of the 8 patients, 2 had APL, 5 AML, and 1 AMML, while morphologies in the 18 patients with DIC and infection were AMML in 8, AML in 7, APL in 2, and AMOL in 1. Although many patients who died of hemorrhage were receiving antibiotics, no specific antibiotic or antibiotic combination seemed

### Table 3. Causes of Death During Initial Four Courses

<table>
<thead>
<tr>
<th></th>
<th>ADOAP or ROAP</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Autopsied</td>
<td>All Patients</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No. (%)</td>
<td>No. (%)</td>
<td></td>
</tr>
<tr>
<td>Total deaths</td>
<td>80 (65)</td>
<td>123 (30)</td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td>38 (48)</td>
<td>60 (49)</td>
<td></td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>7 (9)</td>
<td>14 (11)</td>
<td></td>
</tr>
<tr>
<td>Infection plus hemorrhage</td>
<td>22 (28)</td>
<td>24 (20)</td>
<td></td>
</tr>
<tr>
<td>Organ failure alone</td>
<td>5 (6)</td>
<td>14 (11)</td>
<td></td>
</tr>
<tr>
<td>Multiple</td>
<td>7 (9)</td>
<td>7 (6)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (1)</td>
<td>4 (3)</td>
<td></td>
</tr>
<tr>
<td>Infection, total</td>
<td>66 (83)</td>
<td>90 (73)</td>
<td></td>
</tr>
<tr>
<td>Bacterial</td>
<td>30 (38)</td>
<td>42 (34)</td>
<td></td>
</tr>
<tr>
<td>Fungal</td>
<td>14 (18)</td>
<td>19 (15)</td>
<td></td>
</tr>
<tr>
<td>Bacterial and fungal</td>
<td>14 (18)</td>
<td>14 (11)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>8 (10)</td>
<td>15 (12)</td>
<td></td>
</tr>
<tr>
<td>Hemorrhage, total</td>
<td>32 (40)</td>
<td>41 (33)</td>
<td></td>
</tr>
<tr>
<td>Organ failure, total</td>
<td>12 (15)</td>
<td>21 (17)</td>
<td></td>
</tr>
</tbody>
</table>
associated with an inordinate number of fatal hemorrhages.

Seventeen of the 21 cases of fatal organ failure involved a single organ, and in the remaining cases, 2 organs were affected. Although 30 cases of renal failure (serum creatinine >5 mg/dl or acute oliguria) occurred, 23 of these were closely related to major infections that were the primary causes of death. The probable cause of renal failure in the remaining 7 cases were: aminoglycoside nephrotoxicity (2), bilateral renal vein thrombosis due to DIC (1), urate nephropathy (1), and intrarenal leukostasis (1). In 2 patients the cause was indeterminant.

Of the 28 cases of hepatic failure (bilirubin >5 mg/dl), all but 3 were associated with an underlying infection. In 2 patients, although the possibility of sepsis was considered clinically to be likely, blood cultures were negative and no autopsy was performed. Liver failure was attributed to leukemic infiltration in one patient, although an autopsy was not done.

Seven patients had acute respiratory failure unrelated to hemorrhage or infection. Four of these patients with initial white blood cell counts of 349,000/μl, 329,000/μl, 116,000/μl, and 112,000/μl, respectively, died of respiratory failure in the first 8 days of treatment. Autopsies were performed on 3 of the 4 and showed extensive leukemia infiltration in the pulmonary parenchyma. A fifth patient who died during the third course of treatment had pulmonary infarction caused by large numbers of blasts occluding pulmonary vessels. In two cases, no definite cause was ascertainable.

Six patients died with heart failure as the sole or contributing cause. Three had acute myocardial infarction (one related to occlusion of cardiac vessels by leukemic cells). One patient had nonbacterial thrombotic endocarditis with embolic manifestations, another had congestive heart failure, and the final patient had fatal ventricular fibrillation related to hypocalcemia.

In two patients, acute pancreatitis was the cause of death revealed at autopsy; in neither case was the diagnosis clinically suspected.

Comparison of the Periods 1973 to 1976 and 1977 to 1979

Comparing the periods 1973 to 1976 and 1977 to 1979 for all treated patients, there was a slight decrease in the frequency of death during the first 4 courses of treatment in the later years (31% versus 28%, p = 0.22), but no change in the incidence of death during the first 4 wk of treatment (15% versus 19%, p = NS). The incidence of fatal infection declined from 23% to 19% (p = 0.13), and the incidence of infection as the sole cause of death declined from 17% to 9% (p = 0.01) in the latter period because of a decrease in the incidence of fatal bacterial infection from 18% to 10% (p < 0.06). Conversely, there was no change in the occurrence of fatal fungal infections (8% in both periods). The percentage of all patients experiencing lethal hemorrhage rose from 9% to 13% (p = 0.27) between the two periods, and the incidence of fatal organ failure was unchanged (6% versus 5%, p = NS).

Time of Occurrence of Fatal Events

The incidence of death from hemorrhage was highest during the initial 2 wk (4.2% of all patients), after which it decreased (2% of all remaining patients by weeks 5 and 6). The overall mortality rate, which, as expected, paralleled the incidence of death from infection, began to fall sharply from approximately 10% of all patients per week during the first 8 wk to 5.7% and 2.0% of all remaining patients by weeks 9 and 10 and 11 and 12, respectively. The incidence of fatal fungal infection was relatively constant from the second week of treatment through the eighth week and was no higher during the third than during the first course.

Factors Predicting Causes of Failure

Patients age 50 and over were no more likely to be chemotherapy failures than younger patients (Table 4). However, age did have a profound influence on the incidence of death during the initial four courses. The increased likelihood of death in older patients was largely explained by the increased incidence of fatal infection in these patients. In addition, older patients was more likely to die from hemorrhage and organ failure than younger patients.

Two types of infection prophylaxis were used during these years: laminar air-flow rooms (LAFRs) in combination with prophylactic antibiotics, and prophylac-

| Table 4. Outcome of Remission Induction According to Age |
|------------------------|------------------------|------------------------|------------------------|
| Age < 50 | Age ≥ 50 | No (%) | (%) | p Value |
|------------------------|------------------------|------------------------|------------------------|
| Total | 180 | 193 | 0.24 |
| Fail | 55 (31) | 106 (53) | 0.01 |
| Considered chemotherapy failures | 21 (12) | 15 (8) | 0.24 |
| Died during initial 4 courses | 33 (18) | 90 (45) | 0.01 |
| During first 2 wk | 7 (4) | 30 (15) | 0.01 |
| During first 4 wk | 12 (7) | 57 (29) | 0.01 |
| From infection | 23 (12) | 67 (34) | 0.01 |
| During first 2 wk | 3 (2) | 19 (10) | 0.01 |
| During first 4 wk | 6 (3) | 42 (21) | 0.01 |
| Hemorrhage | 14 (8) | 27 (14) | 0.10 |
| Organ failure | 5 (3) | 16 (8) | 0.04 |
tic antibiotics in standard hospital rooms. Because half of those under age 50 were treated in LAFRs com-
pared to only 5% of those over age 50, and because LAFRs have been shown to protect against fatal in-
feciton, all 378 patients were divided according to
type of infection prophylaxis received. The incidence of
fatal infection in each infection prophylaxis group was
then compared according to age. In each prophylaxis
group there was a twofold higher mortality rate from
infection in patients over than under age 50, becoming
statistically significant due to larger numbers in those
patients who received no infection prophylaxis.

Nineteen of 36 patients considered chemotherapy failures (53%) had antecedent hematologic disorders
(AHDs) compared with only 24 of 217 patients who
entered CR (12%) (p < 0.01). In addition, we found
that patients with antecedent hematologic disorders
had an increased incidence of both fatal fungal and
bacterial infections. Age and AHD are related: 31% of
those ≥50 yr old had AHDs, compared to only 14% of
those under age 50. Therefore, all treated patients
under age 50 were divided into those with and without
AHDs, and the same was done for all patients over age
50. The younger patients with AHDs had a signifi-
cantly higher mortality rate from fungal infection than
patients in the same age group without AHDs (Table
5). The findings were similar to the older patients. A
similar analysis was performed comparing the inci-
dence of fatal bacterial infection in the four groups
(Table 5). Unlike the situation with fungal infection,
the presence of AHDs had little effect on mortality rate
from bacterial infection in patients either over or under
age 50. The incidence of fatal fungal infection was
similar to the incidence of fatal bacterial infection in
patients over age 50 with AHDs, and in younger
patients with this history, the incidence of death from
fungal infection was greater than the incidence of death
from bacterial infection.

We found that an initial white blood cell count
(WBC) of greater than 25,000/μl increased the sub-
vsequent incidence of fatal hemorrhage. We divided all
patients into four groups according to age above or
below 50 and initial WBC above or below 25,000/μl
and compared the incidence of fatal hemorrhage in the
four groups. While 4 of 99 younger patients with lower
WBC counts suffered this complication, 10 of 81 of
similarly aged patients with higher counts did so
(p = 0.07). For older patients, the respective figures
were 9 of 100 and 18 of 98 (p = 0.09). Independent of
age, the totals of 13 of 199 versus 28 of 179 were
significant at the p < 0.01 level. These correlations
were most marked after the initial four weeks of
treatment.

Antileukemic Response

Of 36 chemotherapy failures, only 5 (14%) were
classified as group I (never hypoplastic) (Table 6). The
usual causes of chemotherapy failure were regrowth
of leukemia (group 2B) (13 patients) or PR (group 2D)
(10 patients). In 28 of 123 patients (23%) dying during the initial 4
courses of treatment, no evaluation of response was
possible either because no bone marrow examinations
were performed during the last week of life, no autopsy
was done, or the marrow specimens were inadequate
(Table 6). Of the 95 patients evaluable for response, in
32 (34%) the MLI was never less than 20% (group I).
However, of these 32, 19 (59%) died during the first 3
wk of treatment. Of the 55 evaluable patients surviving
beyond 3 wk, only 13 (24%) were in group I and only 5
(9%) were in group 2B (regrowth of leukemia). Of the
total of 63 patients in whom the MLI was reduced to

<table>
<thead>
<tr>
<th>Resistance Category</th>
<th>Chemotherapy Failure (No.)</th>
<th>Death During First 4 Courses (No.)</th>
<th>Total Failing Patients (No.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I—MLI always &gt;20%</td>
<td>5</td>
<td>32</td>
<td>37</td>
</tr>
<tr>
<td>Group II—MLI reduced to &lt; 20%</td>
<td>31</td>
<td>63</td>
<td>94</td>
</tr>
<tr>
<td>IIA—Hypoplasia at death</td>
<td>0</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>IIIB—Regrowth of leukemia</td>
<td>13</td>
<td>6</td>
<td>19</td>
</tr>
<tr>
<td>IIIC—CR</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>IIIC—PR</td>
<td>10</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>IIIE—Questionable regrowth of leukemia</td>
<td>5</td>
<td>6</td>
<td>11</td>
</tr>
</tbody>
</table>

Persistent pancytopenia, normal marrow differen-
tial 3 0 3
Inevaluable 0 28 28
Total 36 123 159*

*Two patients lost to follow-up not included.
less than 20% (group 2), 50 (79%) died with hypoplastic marrow (group 2A). In the vast majority of the latter patients, the duration of hypoplasia was only 0–2 wk.

DISCUSSION

Over 75% of our failures died before they could be classified as chemotherapy resistant, although some would have been so considered had they survived 4 courses. However, the median time to CR was 6 wk, by which time 80% of the deaths had occurred. Furthermore, two-thirds of those dying after the third week, before which CR is very rare, had marrow hypoplasia. Thus, a considerable number of patients who died could have been expected to enter remission with better supportive care. Evidence was lacking that supportive care had improved between 1973–1976 and 1976–1979. Since the mortality rate did decrease after the first 8 wk, those patients not then in remission could potentially survive higher doses of chemotherapy given at that juncture.

Infection accounted for over 70% of deaths in patients dying during the first 4 courses, the same percent noted in both initial and subsequent remission induction patients between 1954 and 1972. Although the risk of fatal bacterial infection declined during the later years of this study, such was not the case for fatal fungal infections. These, almost uniformly due to Candida sp. and Aspergillus sp., accounted alone or together with bacteria for 37% of infectious deaths. While others have noted 20%–30% mortality from mycoses in acute leukemia, their cases have included a substantial number of patients in relapse. The incidence of this complication during initial remission induction has not been generally appreciated. Only 1 of 200 such patients with AML treated by Tobias et al. died of fungal infection. In addition, the risk of these infections reached its ultimate level as early as the second week rather than later, following bacterial infection and extensive antibiotic treatment. These findings indicate a need for both effective antifungal prophylaxis and early initiation of antifungal treatment in febrile patients.

The 33% incidence of failure due to hemorrhage was unexpected because hemorrhagic mortality has previously been reported to be declining: 67% from 1954–1959, and 37% from 1959–1963 in Hersh et al.’s study and 24% between 1966 and 1972 in Chang et al.’s study. In our patients, fatal hemorrhage was most frequent during the first weeks and was usually associated with infection. Thus, it is unlikely that the observed increase is due to longer infection-free survival.

Severe thrombocytopenia occurred proximate to fatal hemorrhage 83% of the time. However, the early occurrence of such hemorrhage would not incriminate prophylactic platelet transfusion, with its potential for sensitization producing less response to subsequent transfusion. Coagulation abnormalities were present in 63% of patients dying of hemorrhage. Although these abnormalities are generally recognized to be associated with APL, our patients with DIC secondary to the leukemic process were more likely to have other morphologies, although the frequency of APL in cases of DIC due to leukemia (25%) was higher than the frequency of this diagnosis in the total population (5%).

The poorer results in patients over age 50 (45% CR versus close to 70% in those younger) were largely due to early infectious death in those patients. The MRC Working Party in Acute Leukemia in Adults made similar observations. Some (but not others) have maintained that more intensive treatment produces more CRs in older patients by reducing the median time required to attain CR to approximately 4 wk. However, the fourfold increase in mortality rate in the initial 4 wk argues that even with shorter times to CR, elderly patients will remain a prognostically unfavorable group. On the other hand, there was no evidence to suggest that patients over 50 were more chemotherapy resistant than younger patients.

The higher frequency of failure in our patients with an AHD was due to: (1) a higher incidence of resistance to chemotherapy, perhaps reflecting insufficient normal stem cells leading to regrowth of leukemia despite adequate cytoreduction; and (2) a threefold higher mortality from fungal infection—this was independent of age; in fact patients under age 50 with AHDs were more likely to die of fungal than bacterial infection. These results could be explained by quantitative or qualitative immune dysfunction.

Although with improved chemotherapy, high initial WBC count does not decrease probability of remission, our patients with initial counts >25,000/μl suffered more fatal hemorrhage than those with lower initial counts despite routine leukapheresis. Freireich et al. reported an association between a WBC of >300,000 and subsequent intracerebral hemorrhage characterized by destruction of vessel walls by intramural proliferation of blasts. In our study the association of hemorrhage with initial WBC count was highest after the first 4 wk. This suggests that a weakness in vessel walls initially induced by blasts becomes more pronounced with time possibly due to lysis of intramural leukemic infiltrate.

This study emphasizes that further progress in supportive care, especially that given during the first 2 mo.
of treatment, is crucial if initial CR rates are to be increased in AML. Specific strategies should be directed to certain groups of patients. These could include the prophylactic use of new antibacterial and antifungal agents in patients over age 50 and the manipulation of the immune system, as well as prophylactic antifungal treatment, in patients with an AHD. Nonetheless, these patients will still likely be comparatively chemotherapy resistant, thus requiring alternate means of antileukemia therapy.

REFERENCES

Causes of initial remission induction failure in acute myelogenous leukemia

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