CURRENT

HEMATOLOGY AND ONCOLOGY

VOLUME 5

Edited by

Virgil F. Fairbanks

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Preface

Because of readers' enthusiasm for the quality reviews encompassed in *Current Hematology and Oncology,* we have now moved to annual publication. Accordingly, Volume 5 is a little thinner, lighter, and easier to digest than its predecessors. An annual review policy will enable us to ensure that reviews are even more "current" and concise than heretofore.

I thank the many contributors to this volume for their compliance with tight deadlines, for the thoroughness and superior quality of their reviews, and for their great patience with the editor. I also wish to thank the staff of Year Book Medical Publishers for their excellent workmanship, and my secretary, Ms. Sara Brackett, for her endeavors in handling correspondence and typing. Together we have crafted Volume 5 to provide you, the reader, with many hours of informative, and we hope also pleasurable, reading. We believe that *Current Hematology and Oncology,* Volume 5, will fulfill your needs and expectations.

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Contents

CHAPTER 1

Acute Myelogenous Leukemia: Recent Advances in Therapy*

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Acute myelogenous leukemia (AML) is well-known to readers, and has been amply reviewed in volumes 1 and 3 of *Current Hematology and Oncology*, and elsewhere. We have all witnessed considerable improvement in the results of therapy for this disorder during the past few decades, yet AML remains a difficult problem. Studies of AML generate a copious literature and considerable controversy. Treatment continues to evolve gradually. In this chapter I summarize and interpret 250 articles, most published since 1982 that I consider significant recent contributions to our knowledge of this disease and its treatment.

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CLASSIFICATION

Because of the common origin of several hematopoietic cell lines, abnormalities of proliferation and differentiation of red blood cell (RBC) precursors, monocytes, and megakaryocytes occur frequently in AML. The variability in the morphologic features of AML has led to the development of several systems of classification. A widely accepted scheme is the French-American-British (FAB) classification[1–4] (Table 1). Three forms of AML with granulocyte differentiation are identified: acute undifferentiated leukemia (M_1) with evidence of granulocyte differentiation as shown by either 3% or more myeloperoxidase-positive blasts or blasts with a few azurophilic granules, Auer rods, or both; acute myelogenous leukemia (M_2) with maturation to or beyond the promyelocyte stage; and acute progranulocytic leukemia (M_3), characterized by hypergranular promyelocytes with abundant Auer rods. Variant forms of M_3 with minimal granulation and bilobed or multilobed nuclei have been described.[5] As indicated, most if not all cases of M_3 have a specific chromosome abnormality, the t(15;17) translocation. Electron microscopy may be required to identify some microgranular variants. Acute myelomonocytic leukemia (M_4) shows both granulocyte and monocyte differentiation in varying proportions, with at least 20% promonocytes and monocytes in the bone marrow and/or peripheral blood. Acute monocytic leukemia (M_5) shows less than 20% granulocyte components. Two subtypes of M_5 are identified: M_{5a}, poorly differentiated or monoblastic with greater than or equal to 80% immature cells, and M_{5b}, in which promonocytes and monocytes predominate with less than 20% monoblasts. Erythroleukemia (M_6) shows prominent involvement of erythroid precursors. Acute megakaryoblastic leukemia in which immature megakaryocytes with abnormal platelets are prominent is termed M_7.[4]

TABLE 1.
French-American-British (FAB) Classification of Acute Myelogenous Leukemia

DESIGNATION	PREDOMINANT CELL TYPE(S)
M_1 (Undifferentiated myelocytic)	Myeloblasts
M_2 (Myelocytic)	Myeloblasts, promyelocytes, myelocytes
M_3 (Promyelocytic)	Hypergranular promyelocytes
M_4 (Myelomonocytic)	Promyelocytes, myelocytes, promonocytes, monocytes
M_{5a} (Monoblastic)	Monoblasts
M_{5b} (Differentiated monocytic)	Monoblasts, promonocytes, monocytes
M_6 (Erythroleukemia)	Erythroblasts
M_7 (Megakaryocytic)	Megakaryocytes

REMISSION-INDUCTION CHEMOTHERAPY

The initial therapeutic objective in AML is to achieve a hematologic remission: the reduction of leukemia cells to undetectable levels (less than 5% myeloblasts); restoration of bone marrow function including normalization of hemoglobin, granulocytes, and platelets; resolution of hepatosplenomegaly; and return to a normal performance status.[81]

Results of single-agent chemotherapy in AML are summarized in Table 2. The most effective drugs, cytarabine, daunorubicin, and amsacrine, produce remission in 25% to 50% of patients with AML.[6–13] Other anthracyclines such as rubidizione, doxorubicin, aclarubicin (aclacinomycin A), idarubicin (4-demethoxydaunorubicin), and epidoxorubicin are also active, as is mitoxantrone. Lower response rates are observed with cytarabine analogues such as 5-azacitidine, 2-fluro-adenosine monophosphate (2-FAMP) and with the epiodophyllotoxins (etoposide and teniposide). Purine analogues (thioguanine and 6-mercaptopurine) produce remissions in approximately 10% of patients. Response rates to other drugs such as corticosteroids, L-asparaginase, cyclocytidine, cyclophosphamide and other alkylating agents, bisantrene, diaziquone, and conventional doses of methotrexate are less than 10%. Thus, these drugs are generally considered to be inactive. Interferon has not been shown to be active in AML; other biological agents have not been critically evaluated.

Combinations of drugs have been extensively elevated in controlled clinical trials for AML treatment (Table 3). Cytarabine given for five days in combination with marginally effective drugs such as thioguanine or 6-mercaptopurine produce remissions in 35% to 55% of patients.[14–20] The addition of daunorubicin or doxorubicin in this schedule of cytarabine results in complete remissions in 50% to 75% of patients These results are superior to those achieved with less intensive chemo-

TABLE 2.
Single-Agent Chemotherapy in AML

DRUG	COMPLETE REMISSION (%)
Cytarabine	25
Daunorubicin	40–50
Amsacrine	30–50
Mitoxantrone	20
Etoposide	10-20
Thiopurines	10

TABLE 3.
Combination Chemotherapy for AML

REGIMEN	COMPLETE REMISSIONS (%)
Cytarabine + 6-thioguanine or mercaptopurine	35–50
Cytarabine + vincristine + prednisone + cyclophosphamide	30
Cytarabine + daunorubicin + 6-thioguanine (5 days)	50–85
Cytarabine + doxorubicin or daunorubicin (7 days)	35–85
Cytarabine + daunorubicin + 6-thioguanine (7 days)	60–85

therapy. Recently cytarabine treatment has been increased to seven days and combined with three doses of an anthracycline or amsacrine.[21–29] In several large series, remission rates of 65% to 75% have been reported. Although controlled trials comparing anthracyclines are limited, daunorubicin is generally preferred to doxorubicin or other anthracyclines. Daunorubicin is associated with relatively low incidence of cardiotoxic effects at doses less than or equal to 1 gm/sq m.[30] Thus, except in patients with pre-existing cardiac disease, dose modification is rarely necessary. Addition of other drugs to this schedule, such as thioguanine,[31] azacitidine, or etoposide,[32] does not clearly improve results.

A recent prospective randomized trial demonstrated that seven-day courses of cytarabine and daunorubicin are more effective than five-day courses[33]; ten-day courses do not increase remission rates or duration. Nevertheless, several recent studies have used nine or ten days of treatment. Prolonged treatment with cytarabine may be associated with severe gastrointestinal toxic effects.[34] Continuous infusion of cytarabine (100 to 200 mg/sq m/day) and intermittent injections every 12 hours (200 mg/sq m/day) probably produce comparable results. One pilot study suggested a benefit for continuous vs. intermittent infusion but a larger group study showed no difference.[35] A continuous infusion of cytarabine at a dose of 200 mg/sq m/day is reasonable but may require reduction to 100 mg/sq m/day if treatment is prolonged to ten days. In a recent multicenter trial from the Medical Research Council of the United Kingdom (MRC), a five-day course of cytarabine combined with two doses of daunorubicin produced remissions in greater than 70% of patients.[36] The difference between this trial and other studies was that most patients required two or more cycles to achieve remission vs. a single cycle for 60% to 80% of patients receiving more intensive treatment. This difference may be important in older patients unable to tolerate prolonged bone marrow failure. The most recent MRC trial has used a seven-day course of treatment.

In some recent studies, the duration of induction chemotherapy is extended, depending on the extent or rate of reduction of myeloblasts in

the bone marrow six or seven days after initiating chemotherapy. Cytarabine is stopped if the reduction in myeloblasts is greater than 50% to 60% or it may be continued for three additional days at conventional or high doses or with other drugs such as daunorubicin or amsacrine added if a lesser response is detected. This approach has not been validated in controlled trials. Furthermore, there is considerable variability in bone marrow cellularity at different biopsy sites. Because of these considerations individualization of chemotherapy based on bone marrow biopsy results should be regarded as investigational at present.

The optimal dose and schedule of daunorubicin are controversial. One to three daily doses of 30 to 75 mg/sq m have been recommended. Favorable results have been reported at doses greater than or equal to 60 mg/sq m/day for three days in patients younger than 60 years. In one controlled trial, patients older than 60 years had higher remission rates when treated with three days of 30 mg/sq m/day of daunorubicin compared to 45 mg/sq m/day of daunorubicin or 30 mg/sq m/day of doxorubicin; daunorubicin, 60 mg/sq m/day, was not tested.[35] Comparable results have been reported when daunorubicin is given for the first or last three days of cytarabine treatment. One study compared induction regimens consisting of conventional dose cytarabine and thioguanine with either amsacrine or daunorubicin.[37, 38] Remission rates and survival were comparable for the two regimens including patients with acute progranulocytic leukemia who were previously reported to be highly responsive to anthracyclines. Favorable results have also been reported following induction chemotherapy with cytarabine combined with mitoxantrone alone, idarubicin alone, or with a combination of doxorubicin, thioguanine, and etoposide.[39]

High-dose cytarabine has also been used for remission induction in AML.[40–45] Sixty-seven percent complete responses were reported in a recent study of 49 previously untreated patients with adverse prognostic factors who received a three-hour infusion of cytarabine, 3 gm/sq m every 12 hours for four doses; L-asparaginase, 10,000 units, was given four hours later and the treatment was repeated at one week. Similar results have been reported in patients receiving cytarabine, 3 gm/sq m every 12 hours for 12 doses alone or followed by three days of either daunorubicin or amsacrine. This dose of cytarabine has not been evaluated alone in standard-risk patients but a 35% remission rate was reported in one recent group study in high-risk individuals. These data suggest that high-dose cytarabine with L-asparaginase, daunorubicin, or amsacrine may be effective for remission induction. Most recently, high-dose cytarabine has been combined with mitoxantrone. A high remission rate has been reported and toxic effects are said to be less. High-dose cytarabine alone has not been evaluated but is likely to be effective. In other trials, intermediate doses of cytarabine (0.5 to 2.0 gm/sq

m every 12 hours for six doses) produced equivalent results.[46] At present there are no data to indicate that addition of amsacrine or daunorubicin improves results of high-dose cytarabine alone for initial therapy of AML.

Recently, low doses of cytarabine, 10 to 20 mg/sq m/day for ten to 20 days subcutaneously or by continuous intravenous infusion, have been used to treat patients with AML. Most studies involved patients with preleukemia, myelodysplastic syndromes, therapy-linked leukemia, and smoldering AML. Comparatively few patients with typical AML have been treated with low-dose cytarabine.[47–51] Complete remission rates are low (less than 20%) and are usually achieved after substantial cumulative doses of cytarabine (up to 4 gm/sq m). Most patients who achieve remission do so only after bone marrow aplasia. Therefore, the probable mechanism of action of cytarabine in these cases is cytotoxicity rather than induction of differentiation. There is no convincing evidence that low-dose cytarabine is equivalent or superior to cytarabine at conventional or high doses; the low-dose therapy is probably inferior. Nevertheless, selected elderly patients with AML who might not otherwise be treated may benefit from low-dose cytarabine therapy even if remission is not achieved. It may also be useful in settings in which intensive supportive care is unavailable.

In summary, the present consensus holds that the most effective remission-induction regimen is a combination of seven days of cytarabine (200 mg/sq m/day) given by continuous intravenous infusion and three days of daunorubicin. The optimal dose of daunorubicin has not been established. In patients younger than 60 years of age, doses of 45 to 60 mg/sq m/day are recommended; possibly lower doses should be used in patients older than 60 years, but this has not been convincingly determined.

There are presently no data to support extension of the cytarabine infusion to ten days; it is possible that selected patients may benefit. Addition of thioguanine or other agents to optimal doses and schedules of cytarabine and daunorubicin is not likely to improve results. Substitution of amsacrine or possibly mitoxantrone for daunorubicin may produce equivalent remission rates. Although it is possible to use amsacrine in individuals with pre-existing cardiac disease, amsacrine is probably best reserved for postremission therapy. It is likely that similar remission rates can be achieved with high-dose cytarabine alone or combined with L-asparaginase, daunorubicin, amsacrine, or mitoxantrone. Use of appropriate induction chemotherapy regimens should produce remission in greater than 70% of patients. Patients with antecedent hematologic disorders and possibly older patients may have lower response rates, whereas young individuals have remission rates exceeding 80%.

CONSOLIDATION AND INTENSIFICATION CHEMOTHERAPY

Once remission is achieved, the next therapeutic objective is to prevent leukemia recurrence. Relapse is probably related to the persistence of undetectable, possibly resistant leukemia cells. This is sometimes referred to as minimal residual disease. The most common approach to prevention of leukemia relapse is to administer chemotherapy to patients in remission. Several types of postremission chemotherapy have been evaluated, including consolidation, intensification, and maintenance. *Consolidation* usually refers to repeated courses of the same drugs used for remission-induction chemotherapy; it is given shortly after achieving remission. More recently, treatment with non–cross-resistant drugs has been used for consolidation; this is also referred to as *early intensification*. Because of confusion in the use of these terms it may be better to refer to this stage of treatment as *postremission therapy*. However, I shall use the term *consolidation chemotherapy*.

Numerous combinations of drugs at different doses and schedules have been used for consolidation chemotherapy in AML.[19, 20, 28] Usually these add two to six cycles of cytarabine and thioguanine with or without daunorubicin. Occasionally, other drugs such as 5-azacitidine, amsacrine, β-deoxythioguanosine, methotrexate, prednisone, vincristine, cyclophosphamide, doxorubicin, and lomustine (BCNU) have been used singly or in combination. It is difficult to determine what effect these consolidation regimens have on remission duration, since most studies have not included concurrent controls. Nevertheless, the impact has not been substantial since most studies indicate median remission of nine to 16 months regardless of what type of consolidation is given. An exception is a Cancer and Leukemia Group B (CALGB) Trial in which patients received cytarabine and thioguanine at doses producing bone marrow aplasia every 13 weeks for three years. Median remission duration in that study was two years, with approximately 30% long-term leukemia-free survival. In a Southeastern Cancer Study Group (SECSG) trial, patients who achieved remission with cytarabine, daunorubicin, and thioguanine were randomly assigned, for consolidation therapy, either to the same drug combination used for induction or to 5-azacitidine with or without β-deoxythioguanosine. Maintenance chemotherapy, immunotherapy, or both, were given. The longest remissions were observed in patients who received 5-azacitidine for consolidation chemotherapy and cycles of cytarabine and daunorubicin for intensive maintenance therapy. Different results correlated with the composition of the consolidation chemotherapy regimens. These differences will permit design of more effective chemotherapy programs.

In recent studies, remission induction with standard-dose cytarabine and daunorubicin is followed by intensification/consolidation chemother-

apy with high-dose cytarabine with or without daunorubicin. In one preliminary trial, consolidation with one to three courses of high-dose cytarabine and daunorubicin was given to 27 adults with AML in remission; median duration of complete remission was greater than 31 months.[52] This was an uncontrolled trial and patients were entered after being in remission for varying periods. The longest remissions were observed in very young patients; a beneficial effect in older patients (greater than 30 years) was not convincingly demonstrated. Other studies have reported less favorable results not substantially different from those achieved with more conventional consolidation schemes.[53]

An uncontrolled study suggested that a single cycle of consolidation chemotherapy substantially increased the proportion of patients remaining in continuous complete remission at two years compared to patients receiving identical induction chemotherapy without consolidation.[54] Other uncontrolled trials, primarily in children, have suggested a high proportion of long-term survivors following intensive postremission chemotherapy.[22, 23, 55] The statistical interpretation of these studies has been controversial; the results require confirmation. An uncontrolled trial in adults involving intensive therapy and splenectomy also yielded favorable long-term results.[56]

The role of consolidation and/or early intensification therapy of AML is unknown.[57] Surprisingly, there have been few randomized trials of consolidation chemotherapy in AML. In an Eastern Cooperative Oncology Group (ECOG) study of 146 patients, those who received consolidation chemotherapy had a median remission duration of 40 weeks vs. 34 weeks for the controls. This difference was not statistically significant, but nonetheless leads us to favor use of consolidation therapy.[58] The proportion of patients in remission at two years was higher in patients receiving consolidation (30% vs. 14%) but only 14 patients were analyzed and again the difference was not statistically significant. Analysis of this study suggests that if there is benefit from consolidation chemotherapy it is by increasing the proportion of long-term survivors rather than by increasing the median duration of remission. One reservation is that relatively low doses of consolidation chemotherapy were given: more impressive results might have been observed with more intensive treatment. A second randomized trial in 56 patients failed to show benefit of consolidation chemotherapy in either median remission duration (43 vs. 48 weeks) or long-term survival.[59]

In summary, there are no convincing data that consolidation chemotherapy or early intensification is of benefit in AML. Nevertheless, two practical considerations support its use. First, experimental and clinical data indicate that induction chemotherapy alone is unlikely to cure more than a small proportion of patients with AML. A second consideration is the lack of well-designed studies that evaluate high-dose con-

solidation therapy in patients who receive intensive induction chemotherapy. Until such data are available, it is reasonable to administer one to three cycles of consolidation/early intensification chemotherapy to patients with AML in remission. Whether this should consist of the same drugs used for remission induction or new drugs is unknown. A reasonable strategy is to give one cycle of the same drugs and a second and/or third cycle with active and possibly non–cross-resistant effective drugs. Examples of the latter include high-dose cytarabine, amsacrine, or possibly 5-azacitidine. Investigational drugs, such as the anthracyclines, etoposide, mitoxantrone, and harringtonine, may also be considered. At present, my associates and I administer two cycles of consolidation chemotherapy. The first cycle consists of high-dose cytarabine (3 gm/sq m every 12 hours for eight doses) and daunorubicin (45 mg/sq m/day for three doses); the second cycle is conventional-dose cytarabine (100 mg/sq m every 12 hours for seven days) and daunorubicin (45 mg/sq m/day on days 5, 6, and 7). Our preliminary results have been favorable.[60] A reasonable alternative is a six-day course of high-dose cytarabine followed in four weeks by a five-day course of amsacrine with or without a third cycle of conventional-dose cytarabine and daunorubicin or mitoxantrone.

MAINTENANCE CHEMOTHERAPY

For maintenance chemotherapy following remission, patients are given lower doses of drugs for one to three years. The value of maintenance chemotherapy has been questioned. We recently reviewed data from 1,491 patients who were randomly assigned to receive either maintenance chemotherapy, immunotherapy, both, or neither.[61] Median remission duration and survival were identical for the four groups. Furthermore, median remission duration has remained relatively constant (nine to 16 months) between 1970 and 1980 despite the use of maintenance regimens differing markedly in drug composition, complexity, and intensity.[19, 20, 28] One exception is a CALGB trial in which subcutaneous cytarabine was shown to be superior to intravenous administration when used for maintenance.

Several recent studies at our center, from Switzerland, the United States (Maryland), England, and West Germany used intensive induction and consolidation chemotherapy without maintenance chemotherapy.[54, 62–67] Median remission duration in these studies was 16 months and 26% of patients remained in continuous complete remission for longer than three years. These results are not different from those of trials using maintenance chemotherapy.

There have been few randomized trials of maintenance chemotherapy