Chemotherapy for Patients with Acute Myeloid Leukemia in First Remission

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Introduction

Acute myeloid leukemia (AML) is a heterogenous group of diseases characterized by malignant transformation of hemopoietic stem and progenitor cells in the bone marrow, resulting in failure of bone marrow function and ultimately (without effective therapy) death from anemia, infection, and bleeding. In the last decade there has been progress in understanding the molecular pathogenesis of some of these diseases, particularly acute promyelocytic leukemia (APL) and those cases with core binding factor (CBF) abnormalities, but for the majority of patients there is still little insight into the causes of AML. From a clinical perspective, the biologic heterogeneity of AML is important in dictating therapy and in determining prognosis. The two major prognostic factors—to a certain extent interlinked—are cytogenetic abnormalities in the leukemic cells and age at diagnosis. There are three major cytogenetic risk categories [1,2]:

- **favorable risk**, comprising APL with t(15;17) and cases with CBF abnormalities
- **intermediate risk**, with normal karyotypes or cytogenetic abnormalities not listed in the other categories
- **poor risk**, including abnormalities of chromosomes 5 or 5q, 7, 3q, and cases with complex karyotypes

APL and CBF cases tend to occur in younger patients; cytogenetic changes in the poor-risk category are more common in the elderly.

The initial phase of treatment of AML, induction chemotherapy, usually involves two main classes of drugs: cytarabine and one of the anthracyclines, such as daunorubicin or idarubicin. Treatment of unselected patients with the “7&3” regimen, consisting of a 7-day continuous infusion of cytarabine at a dose of 100 to 200 mg/m² per day and daunorubicin at a dose of 45 to 50 mg/m² intravenously daily for 3 successive days, results in complete remission in 60% to 65% of patients [3]. Lower response rates are seen in patients over 55 to 60 years of age, or in those with poor-risk cytogenetics. The addition of other drugs, such as thioguanine or etoposide, does not appear to improve remission rates but may improve long-term leukemia-free survival in those who achieve remission [4]. Nor does intensification of the dose of cytarabine in induction increase the complete remission rate, but it does have a favorable effect on remission durability in those achieving a response [5]. Other agents, including newer, targeted forms of therapy such as gemtuzumab ozogamicin (Mylotarg®, Wyeth Pharmaceuticals, Philadelphia, PA) or FLT3 inhibitors, have not yet been proven to have a role in induction therapy for AML [6,7].

Given that the majority of patients with newly diagnosed AML achieve a complete remission with induction therapy, the major challenge that needs to be confronted is how to prevent recurrence of the disease. Unfortunately, most patients still experience a relapse and ultimately die of their disease. Design of new strategies to deal more effectively with residual leukemia after successful induc-
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Strategies for Therapy after Remission
The need for further chemotherapy following the attainment of a complete remission after initial induction therapy is based on relatively small clinical trials carried out two decades ago, comparing repeated courses of low doses of cytarabine and thioguanine to no further treatment; a prolongation of remission was demonstrated [8]. This finding has shaped the design of therapeutic strategies in AML since the 1980s, with general acceptance of the need for some form of postremission treatment. The strategies that have been subsequently developed include:

- consolidation therapy using attenuated courses of the drugs used for induction, or intensified with high-dose cytarabine
- myeloablativ chemotherapy with or without total body irradiation, followed by hemopoietic rescue with cryopreserved autologous stem cells
- allogeneic stem cell transplantation using histocompatible related or unrelated donors
- prolonged low-dose maintenance chemotherapy
- immunotherapy

Consolidation therapy
Consolidation therapy is usually defined as treatment given early after remission is attained, delivered in courses of at least moderate intensity and anticipated to cause significant myelosuppression, with the aim of producing further substantial leukemic cytocruduction. Consolidation therapy often involves the use of attenuated courses of the same drugs used in the induction phase of treatment, but may also incorporate higher doses of these drugs, or alternative chemotherapeutic agents that potentially are not cross-resistant.

The evidence for the value of consolidation therapy dates back to the 1980s. A randomized trial by the Eastern Cooperative Oncology Group (ECOG) showed a major prolongation in remission duration with consolidation therapy followed by low-dose maintenance, compared with maintenance alone [9]. On this basis, consolidation therapy has been accepted as standard practice. The optimal choice of drugs, their dosage, and the number of treatment courses necessary has required further study, however.

Consolidation therapy after conventional induction therapy
The main breakthrough came with the report from Mayer and colleagues from the Cancer and Leukemia Group B (CALGB) [10•], describing the use of high-dose cytarabine after remissions induced by conventional-dose cytarabine and daunorubicin. Patients aged 60 years or less receiving cytarabine at a dose of 3 g/m² every 12 hours on days 1, 3, and 5 of each course for a total of 4 courses had a 44% probability of remaining in remission at 4 years. In comparison, the probability was 29% for patients randomized to receive 5-day infusions of cytarabine at 400 mg/m² daily, and 24% for those who received 100 mg/m² on the same schedule. Only 62% of patients randomized to the high-dose cytarabine arm were able to receive the full four courses, however, compared with 76% and 78% of patients treated at the lower doses. The toxic death rate for the high-dose arm was 5%. Patients over 60 years of age did not benefit from high-dose cytarabine, with less than half receiving more than one course.

A study by ECOG compared maintenance therapy for 2 years with a single course of cytarabine 3 g/m² every 12 hours for 6 days, plus amsacrine [11]. The toxic death rate was 12% in the high-dose consolidation arm, but leukemia-free survival was improved in patients under 60 years of age (28% versus 15% for those given maintenance therapy).

A subsequent study by ECOG and the South West Oncology Group (SWOG) [12], comparing high-dose cytarabine-based consolidation with autologous or allogeneic stem cell transplantation in first remission, showed comparable results for intensive consolidation therapy. Patients receiving a single course of 12 doses of high-dose cytarabine had an actuarial 4-year leukemia-free survival of 35% in this study.

Finally, a recently reported study by the CALGB [13•] compared three cycles of high-dose cytarabine (in the previously described schedule [10•]) to three cycles of multi-agent chemotherapy (high-dose cytarabine alone, high-dose cyclophosphamide and etoposide, and mitozantrone plus diaziquone). The 5-year leukemia-free survival for the high-dose cytarabine arm was 35%, comparable with the group receiving multi-agent chemotherapy (30%).

The only study not to show a substantial benefit of high-dose cytarabine in consolidation was reported by the SWOG [14]. Within this complex trial, a cohort of patients received induction therapy with standard-dose cytarabine plus daunorubicin and thioguanine (DAT), then were randomized to consolidation therapy with either two courses of standard-dose cytarabine plus daunorubicin or one course of cytarabine 3 g/m² (later modified to 2 g/m²) for 10 doses. Leukemia-free survival was 24% for the standard-dose arm but only 20% and 14% for the 3-g and 2-g dose arms, respectively.

These studies highlight a number of very important issues:

- With the single exception of the SWOG trial [14], four studies have shown leukemia-free survivals in the range of 28% to 44% for various schedules of high-dose cytarabine, statistically superior in two studies compared with standard-dose consolidation regimens.