Review Article

Acute Myeloid Leukemia: An Overview

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ABSTRACT Acute myeloid leukemia (AML), a cancer of myeloid line of cells, is characterized by rapid proliferation of abnormal cells which accumulate in the bone marrow and consequently interfere with the production of normal blood cells. Major advances in the understanding of leukemogenesis have been made by the characterization and the study of acquired cytogenetic abnormalities. However, the care of a patient with AML unfortunately involves several challenges. First, the diagnosis must be confirmed with a classification of the clinically relevant subtype. Second, a higher prevalence of co-morbid conditions as well as the unique biological features of AML patients account for the relatively poor response to therapy. Finally, it's a big challenge to keep the patient in complete remission (CR) for longer duration and to decrease the rate of relapse. AML is a potentially curable disease but only a minority of patients is cured with current therapy. Areas of active research in AML include the elucidation of the cause of AML, the identification of better prognostic indicators, the development of new methods of detecting residual disease after treatment, and development therapies. In this review we discuss the poignant, historical aspects of AML, the classification and prognostic factors of AML and the current methods of systemic leukemia therapy. A major objective of our research is to understand the current available treatment options and their effectiveness in different groups of patients. For these objectives we reviewed the literature available in the last 30 years.

KeyWords: AML, Prognostic factors, Induction therapy, Complete remission

Back ground

Unfortunately, untreated acute myeloid leukemia is a uniformly fatal disease with a median survival time of less than 3 months. In the United States, the annual incidence of AML is approximately 2.4 per 100,000 persons and it increases progressively with age, to a peak of 12.6 per 100,000 adults 65 years of age or older (1). Despite the improvement in overall survival time in the last couple of decades, only a small percentage of patients achieve a long term disease free survival. Thus, the treatment of AML is unsatisfactory. Further, the CR rates and median survival time of an unselected population of patients may be lower than what is reported in clinical trials.

The diagnosis of AML is established in most cases by a bone marrow aspirate that demonstrates at least 30% blast cells (2). The traditional criteria to distinguish between AML and acute lymphoblastic leukemia (ALL) rely on morphology and cyto-chemical reactions. The subtypes of AML must be recognized at the time of diagnosis because of the different treatment lines available for the specific types of AML.

Identification of prognostic factors after the diagnosis may allow one to estimate the likelihood of an outcome and to determine the optimal treatment strategy. The appropriate treatment can be defined as that which provides the patient with the greatest potential benefit of therapy without undue treatment-related morbidity or mortality. Undoubtedly, the current medical therapies provide a significant increase in the survival rates but most of the patients with AML; however ultimately die because of the disease or complication from the treatment. Induction therapy for AML is a treatment intended to achieve induction of CR. CR is defined as the absence of morphological evidence of leukemia after recovery of the peripheral blood cell counts. Post remission therapy is treatment administered in CR to prevent or delay the relapse of leukemia (3). However, majority of the patients do have disease relapse. The failure to achieve CR or the occurrence of relapse despite post remission therapy may be related to resistance to the chemotherapy. Intensification of therapy is a treatment strategy designed to overcome resistance to chemotherapy (3). Results of many clinical trials of intensified induction or post remission therapy suggest improved out come. However treatment related morbity and mortality of dose intensification may be substantial and may limit any potential benefit.

The goal of this review is to provide a rationale for selecting ap

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propriate treatment for a given patient. One needs to avoid unnecessary or unproved treatment modifications for patients with a reasonable likelihood of benefiting from conventional therapy. Because the risks and benefits of alternative treatment strategies are uncertain for most patients, a systematic approach for the evaluation of clinical trials should be used.

Classification

The French-American-British (FAB) classification system divided AML into 8 subtypes, M0 through to M7, based on the type of cell from which the leukemia had developed and its degree of maturity (Table 1). These subtypes are characterized by degree of granulocytic maturation (M1, M2 and M3) or monocytic differentiation (M4 and M5) or by the presence of large numbers of erythroblasts (M6) or megakaryoblasts (M7) (4).

The World Health Organization (WHO) classification of acute myeloid leukemia (Table 2) attempts to be more clinically useful and produce more meaningful prognostic information than the FAB criteria (17).

Table 1 French-American-British (FAB) classification system

Type	Name	Cytogenetics (% of cases)
M0	Minimally differentiated acute myeloblastic leukemia	inv (3q26)& t(3;3) (1%)
M1	Acute myeloblastic leukemia, without maturation	t(9;22)
M2	Acute myeloblastic leukemia, with granulocytic maturation	t(8;21)(40%) , t(6;9)(1%)
M3	Promyelocytic, or acute promyelocytic leukemia(APL)	t(15;17)(98%), t(11;17)(1%), t(5;17)(1%)
M4	Acute myelomonocytic leukemia	11q23(20%), inv(3q26), t(3;3)(1%), t(6;9)(1%)
M4eo	Myelomonocytic together with bone marrow eosinophilia	inv(16), t(16;16)(80%)
M5	M5a: Acute monoblastic leukemia; M5b: Acute moncytic leukemia	11q23(20%), t(8;16)(2%)
M6	Acute erythroid leukemia's	
M7	Acute Megakaryoblastic leukemia	t(1;22)(5%)

Table 2 World Health Organization (WHO) classification

Name	Description
AML with characteristic genetic abnormalities	AML with t(8;21) AML with inv(16) AML with t(15;17) Patients with AML in this group have a high rate of remission and a better prognosis compared to other types of AML
AML with multilineage dysplasia	This category includes patients who have had a prior myelodysplastic syndrome (MDS) or myelodysplastic disease that transforms into AML. This category of AML occurs most often in elderly patients and often has a worse prognosis.
AML and MDS therapy related	This category includes patients who have had prior chemotherapy and/or radiation and subsequently develop AML. These leukemia's may be characterized by specific chromosomal abnormalities and often carry a worse prognosis.
AML not otherwise categorized	Includes subtypes of AML that do not fall into above categories.

Prognostic Factors

Identification of prognostic factors may allow one to estimate the likelihood of an outcome, to determine an optimal treatment strategy. If used judiciously, prognostic factors are considerable value in treatment decisions. The age of the patient, at the time of diagnosis, leukemic cell Karyotype, and whether the leukemia is de novo or secondary are well established factors that influence the treatment decisions.

Age is the strongest independent predictors of prognosis in acute leukemia. The likelihood of achieving CR is reduced with increasing age. This poor outcome in elderly is due to two factors. First, there is reduced tolerance to the rigors of chemotherapy and the period of myelosuppression. Second, resistance to chemotherapy is frequently observed.

In some cases patients with newly diagnosed AML have had

myelodysplasia or exposure to cytotoxic agents. Exposure to cytotoxic agents accounts for approximately 10-20% of cases of AML. The overall prognosis of the patients with therapy-related AML is poor (5). Age, overall performance status and the status of the co morbid conditions including other malignancies frequently limit the ability to treat the disease.

In AML, three cytogenic findings consistently appear to be associated with a high likelihood of CR: t (8; 16), inv (16), or t (15; 17) (3). The majority of the patients with these translocations are younger and present with de novo AML. The patients with favorable cytogenetic findings in general are not thought to be candidates for bone marrow transplant in CR. The 8; 21 translocation occurs in 8% to 10% of the cases of AML (6). The CR rate for patients with this abnormality is greater than 90%. An abnormality involving chromosome 16 occurs in fewer than 4% of the cases and is uniformly associated with the syndrome of acute myelomonocytic leukemia with abnormal eosinophils (7). The most common abnormality is inversion of the short and long short arms of chromosome 16 that is inv (16) (p13q22). Deletions in long arm of chromosome 16 do not confer a favorable prognosis (8).

Abnormalities that involve loss or deletion of chromosomes 5, 7 or both have been associated with a low likelihood of achieving CR and a brief remission (9). Translocations involving 11q23 have been reported to have poor prognosis. Patients with leukemia cells with residual normal metaphase appear to do better than those in which all blast cells have an abnormal metaphase state. Patients with secondary AML and 1 1q23 abnormalities are very unlikely to achieve CR or survive more than 2 months with conventional therapy (10).

By combining these prognostic factors, one can divide AML into three broad prognostic groups: favorable, standard (intermediate), or unfavorable prognostic subgroups (4).

The favorable prognosis subgroup, which includes approximately 20 percent of cases among the patients who are 60 years of age or younger, is defined by the presence of leukemic blasts with the t (15; 17), t (8; 21), or inv (16) mutation or molecular evidence of these abnormalities. These mutations have high rates of complete remission and a relative low risk of relapse (30 to 40 percent) (4).

At the other end of the spectrum is the unfavorable prognostic subgroup, which includes approximately 15 percent of the cases between 15 to 60 years of age. These cases are defined by the presence of leukemic blasts with cytogenic abnormalities involving more than two chromosomes, monosomies of chromosome 5 or 7, deletion of long arm of chromosome 5 or abnormalities of long arm of chromosome 3. These chromosomal abnormalities are more common in elderly patients with AML or in the patients with secondary AML. This group represents a considerable therapeutic challenge for which no current treatment approach is satisfactory (4).

Between these groups are patients who are characterized as having an intermediate risk of relapse. The leukemic blasts of these patients have either a normal Karyotype or cytogenetic abnormalities that are not included in the definition of the other subgroups (4).

Treatment

The primary objective in treating patients with AML is to induce remission and thereafter prevent relapse.

Induction of remission

Induction therapy for acute leukemia is treatment intended to achieve induction of CR. CR is conventionally defined morpholog ically by the presence of fewer than 5 percent blasts in bone marrow together with the recovery of peripheral-blood counts.

Cytarabin (ara-C) and Anthracycline (daunorubicin or idarubicin) have been the backbone of treatment to induce remission. The dose of ara-C is 100-200 mg/square meter of the body as a continues intravenous infusion over 24 hours for 7 days. The traditional Anthracycline is daunorubicin, which is given 30-60 mg/square meter of the body as a brief intravenous infusion daily on the first three days (Table 3) (11). Induction chemotherapy usually requires a hospitalization of about 1 month to receive the chemotherapy and recover from its side effects. A bone marrow aspirate is obtained 1 or 2 weeks after completion of ara-C infusion. If the bone marrow demonstrates a persistent leukemia, then a second cycle of therapy is administered. If there is a marrow hypoplasia or if findings are equivocal, then marrow aspirate should be obtained and examined periodically to judge recovery. With the use of daunorubicin and cytarabine complete remission can be routinely induced in 70 to 80 percent of patients who are 60 years of age or younger and in approximately 50 percent of older patients. Approximately 30% of the patients who achieve CR require additional courses of induction therapy (11).

Table 3 conventional induction of remission

"3" & "7"approach to remission induction	
Cytarabine	Continues IV infusion (24 hours) for seven consecutive days 40-60 mg per square meter of body surface area
Anthracycline	Iv push (15-30 mins) for three consecutive days 100-200 mg per square meter of body surface area

Induction regimens administered to younger patients have been modified to address resistance to therapy. These modifications include: a) use of an alternative Anthracycline, b) administration of agents in addition to ara-C and daunorubicin, or c) substantial increase in the dose of ara-C (3). These approaches are not generally feasible in older patients because of reduced tolerance to the toxic effects of the chemotherapy.

The addition of ectoposide to the standard induction therapy dose not increases the CR rates but dose increase the median duration of CR in younger patients. There is also a trend of increased overall survival for patients who receive ectoposide (12). The use of high dose of ara-C i.e. 3 g per square meter twice a day dose not increases the rate of remission but do favorably influence relapse and survival (13).

Induction therapy usually requires adequate cardiac, hepatic and renal function monitoring. The goal of the induction phase is to reach complete remission. Complete remission does not mean that the disease has been cured; rather it signifies that no disease can be detected with available diagnostic methods i.e. < 5 % leukemic cells remain in the bone marrow after induction therapy.

Secondary AML

The patients with newly diagnosed AML may have had myelodysplasia or exposure to cytotoxic agents. The most common characteristics of therapy-related AML are: 1) prior treatment with an alkylating agent, 2) prodromal preleukemic phase, 3) a complex Karyotype typically involving chromosomes 5, 7 or both (5). The prognosis of therapy-related or secondary AML is poor. The conventional induction therapy used in de novo AML produces fewer than 20% CR. The most promising results have been observed with high dose ara-C during induction therapy. CR rates range from 25% to 50% with a median survival time shorter than 6 months and very few survival at 1 year (5). The intensified induction therapy may be warranted for patients with good performance status. The majority of patients with secondary AML are probably best treated with supportive care or encouraged to enroll in an investigational trial.

Therapy for Acute Promyelocytic Leukemia (APL) (M3)

APL accounts for 10% of cases of AML. The morphology of this leukemia is distinct, with predominance of dysplastic promyelocytes having large, coarse granules. The clinical presentation of APL is frequently complicated by disseminated intravascular coagulation, which increases the rate of early death. The disease free survival is favorable for patients who achieve CR. APL is considered separately from other subtypes of AML because of sensitivity of leukemia to oral all-trans-retinoic acid (ATRA). The initial experience with ATRA in the treatment of APL showed that 95 % of CR can be achieved in newly diagnosed APL (14).

An important complication that may occur during induction therapy with ATRA is retinoic acid syndrome. This syndrome is characterized by fever, fluid retention, pulmonary infiltrates with hypoxemia and rarely, failure of multiple organs. This established syndrome is treated with dexamethasone and ATRA is discontinued (15).

At present combination of ATRA and an Anthracycline during induction therapy of APL is reasonable. Patients in CR should receive conventional chemotherapy.

Older patients with AML

More than three fourth of patients with AML are older than 60 years. In this age group, there is uneven distribution of unfavorable prognostic factors (e.g., cytogenic abnormalities, features of drug resistance, or a history of myelodysplastic syndrome). In addition, older patients cannot tolerate intensive chemotherapy well. Currently, patients older than 60 years of age who have a good performance status and meet the medical criteria of adequate organ function are usually offered induction chemotherapy and have an overall probability of complete remission of 50 percent. Among those with a complete response, approximately 20 percent survival free of leukemia for at least two years. Patients who have cytogenetic abnormalities and high white cell count at presentation, who are more than 80 year of age, and who are in poor general physical condition have a low likelihood of complete remission. High-dose chemotherapy is highly unlikely to improve the clinical outcome in older patients. No doubt, new approaches to therapy are needed to improve the cure rates in this large cohort of patients.

Post induction therapy

Once remission is induced, further intensive treatment of AML patients is essential to prevent relapse. Conventional post induction therapy comprises consolidation and maintenance. Consolidation therapy in AML consists of treatment doses that are equivalent to or higher than those administered in induction therapy. Maintenance therapy in AML generally involves administration of less myelosuppressive treatment for prolong periods.

Allogenic bone marrow transplantation is the most effective anti-leukemic treatment currently available for the young patients. The risk of relapse among patients in first complete remission who receive an HLA-matched transplant from a sibling is generally less than 20 percent. The reduced relapse rate is the result not only of the use of marrow-ablative high dose cytotoxic therapy before bone marrow transplantation, but also of the allogeneic effect mediated by the graft against leukemia in the host (graft-versus-leukemia effect). However, this favorable effect is partially offset by the toxicity of treatment and mortality related to the complications of immunosuppression (16).

Myeloablative treatment supported by autologous stem cell transplantation has been widely used in recent years. Many studies indicate the survival rates of 45 to 55 % with autologous bone mar

row transplant (16). Many studies didn't find much difference between the allogenic and autologous bone transplantation in terms of patient survival.

Relapse

Approximately 75% of patients with AML who achieve CR have relapse. The likelihood of relapse is influenced by a variety of factors including age, cytogenic findings, and initial leukocyte count. Relapse normally occurs within the bone marrow and involvement of an extra-medullary site is usually simultaneous with relapse in the marrow. The majority of the patients usually die of acute leukemia or complications of salvage therapy.

For patients with relapsed AML, the only proven potentially curative therapy is a stem cell transplant (16). For children and younger adults who have a first relapse or those who don't have a complete response to first line induction therapy, the recommended option is marrow-ablative (high dose) cytotoxic treatment followed by hematopoietic stem cell transplantation, including autograft or allograft from genotypically HLA-matched related donors or phenotypically HLA matched unrelated donors. Currently, the survival rate after either autologous transplantation or allogenic transplantation with HLA-matched donors for patients with AML in first relapse or second remission is about 30 percent (16).

Supportive care

A. Replacement of blood products

Patients with AML have a deficiency in the ability to produce normal blood cells and therefore need replacement therapy. In addition, chemotherapy further worsens this deficiency.

Packed red blood cells are given to patients with a hemoglobin level of less than 7-8 g/dl or at a higher rate if the patient has significant cardiovascular disease.

Platelets should be transfused if the levels are less than 10,000-20,000 cells/ul. Patients with pulmonary or gastrointestinal hemorrhage should receive platelets transfusions to maintain a value greater than 50,000 cells/ul. Patients with CNS hemorrhage should be transfused until they achieve a platelet count of 100,000 cells/ul.

Fresh frozen plasma should be given to patients with a significantly prolonged prothrombin time, and cryoprecipitate should be given if the fibrinogen level is less than 100 g/dl.

B. Antibiotics

Intravenous antibiotics should be given to all febrile patients. Antibiotics should include broad spectrum coverage such as that provided by a third generation cephalosporin with or without vancomycin. Patients with persistent fever after 3-5 days of antibacterial antibiotics should receive antifungal medicines.

Prophylactic antibiotics should be used in non febrile patients undergoing intensive chemotherapy. A commonly used regimen is ciprofloxacin, fluconazole or itraconazole and acyclovir or valacyclovir. Once patients receiving these antibiotics become febrile, the regimen is changed to intravenous antibiotics.

C. Allopurinol

Allopurinol at 300 mg should be given 1-3 times a day during induction therapy until the clearance of blasts and resolution of hyperuricemia. For patients who cannot tolerate oral medications, intravenous drugs such as rasburicase are an option. Rasburicase should also be considered in patients at high risk of sever tumor lysis (very high LDH, baseline renal insufficiency).

D. Use of hematopoietic growth factors

G-CSF and granulocyte-monocytes colony stimulating factor (GM-CSF) can stimulate the production and activation of granulocytes and monocytes and promote their mobilization from the bone marrow to the blood circulation. The duration of neutropenia is consistently shorter with the use of either of the cytokines. In the light of many studies, it has been proved that neither G-CSF nor GM-CSF has a standard role in the clinical care of patients with AML. However, it has been proven that use of these cytokines might be justified in patients with serious infections that do not respond to antimicrobial treatment.

Conclusion

The majority of the patients with AML in CR will ultimately have relapse. The prognosis of most of the patients is poor. The longer the duration of first CR, the higher the likelihood of response to reinduction therapy and a durable second CR. Still today, BMT is the preferred approach because patients treated with non-myeloablative therapy have limited disease free survival. Recent developments in understanding the biology of AML have provided multiple targets for developing agents with potential activity against the disease. It is likely that a number of these agents, singly or in combination, will be effective against subgroups of patients with AML. It is also likely that these agents will complement traditional and newly developed cytotoxic agents used for treating AML. New strategies, such as maintenance therapy to suppress minimal residual disease using one or more of these agents, may prove effective in improving survival.

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Invitation from the President

If you have never been to Australia before now is your chance to come. If you have been before then come and explore our wonderful country again but this time come to learn with us all about how we can help improve the outcomes for all of our patients in what I hope will be a warm, collegial and friendly congress.

Why Australia one might ask? Well it's safe, relatively cheap with totally friendly people. We have organised great accommodation in the best places at the sites around Australia at all pricing levels. The air is clean, the environment pristine and the animals fascinating.

The main congress will be held in Darling Harbour, Sydney just a stones throw from the famous Opera House and the Sydney Harbour Bridge. The congress here will emphasise and involve members of other discipline areas so we can all learn together in a relaxed environment.

The major foci will revolve around the theme areas of lymphangiogenesis, lymphatics, lymphoedema and life, that is from the molecular level to the holistic one. Our aims will be to explore what we can do better in terms of early detection of lymph and other oedemas, their prevention, new directions in treatment and management and how we can better do these by working and learning together.

Importantly we will have a strong emphasis on what our younger lymphologists and students in other discipline areas can tell us. We will welcome innovation and novel ideas.

For those interested in seeing a little more of Australia, you can come to the Pre congress Satellite meeting to be held in Cairns, which is situated in Far North Queensland on the Great Barrier Reef. Here our focus will be on tropical diseases, heat and humidity and its effect on the lymphatic system. There will be time to visit the reef and dive and sail or just enjoy the environment there.

If you want to see still more of Australia then come to the Post Congress Satellite meeting which will be held in Central Australia at Ayers Rock (now called Uluru). Here you will watch the sun set on the "Rock" and have a chance to participate in discussions about rural and remote health issues with respect to lymphoedemas, the effect of dry on the lymphatics and most exciting of all have an opportunity to interact with Australian and New Zealand Phlebologists who will also have a common day with us in Central Australia.

We are very excited to have this congress in Australia and want to proudly show you all our country, our people and introduce you to our researchers.

Bring your partner, your family, your friends, I and our congress organisers will make sure it will be a memorable experience for all. Book in early to get the best deals!

We look forward to seeing you at the 22nd International Society of Lymphology Congress in Australia in 2009.

Professor Neil Piller
Congress President

Congress Organisers

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