



Ockham Technical Synopsis is a recurring series prepared for internal staff and consultants of Ockham Development Group Inc. (Ockham). Highlighting current and emerging issues and challenges in clinical research, these publications are intended to disseminate intelligence captured during the execution of key clinical trials and are therefore updated on a continuous basis.

ACUTE MYELOID LEUKEMIA (AML)

NATURAL HISTORY AND OUTCOME

Disease Definition

Treatment advances in adult Acute Myeloid Leukemia (AML) – also known as Acute Myelogenous Leukemia – have resulted in substantially improved complete remission rates and five-year survival (SEER). Treatment should be sufficiently aggressive to achieve complete remission because partial remission offers no substantial survival benefit. Approximately 60% to 70% of adults with AML can be expected to attain complete remission status following appropriate induction therapy. More than 15% of adults with AML (about 25% of those who attain complete remission) can be expected to survive three (3) or more years and may be cured. Remission rates in adult AML are inversely related to age, with an expected remission rate of >65% for those younger than 60 years.

Data suggest that once attained, duration of remission may be shorter in older patients. Increased morbidity and mortality during induction appear to be directly related to age. Other adverse prognostic factors include central nervous system involvement with leukemia, systemic infection at diagnosis, elevated white blood cell count ($>100,000/\text{mm}^3$), treatment-induced AML, and history of myelodysplastic syndrome. Leukemias that express the progenitor cell antigen CD34 and/or the P-glycoprotein (MDR1 gene product) have an inferior outcome.

Successful treatment of AML requires the control of bone marrow and systemic disease and specific treatment of central nervous system (CNS) disease, if present. The cornerstone of this strategy includes systemically administered combination chemotherapy. Because only 5% of patients with AML develop CNS disease, prophylactic treatment is not indicated.

Treatment is divided into two phases: Induction (to attain remission), and Post-Remission (to maintain remission). Maintenance therapy for AML was previously administered for several years but is not included in most current treatment clinical trials in the United States. Other studies have used more intensive consolidation therapy administered for a shorter duration of time after which treatment is discontinued. Consolidation therapy appears to be effective when given either immediately after remission is achieved or when delayed for nine months.

The classification of AML has been revised by a group of pathologists and clinicians under the auspices of the World Health Organization (WHO). While elements of the French-American-British classification have been retained (i.e., morphology, immunophenotype, cytogenetics and clinical

features), the WHO classification incorporates more recent discoveries regarding the genetics and clinical features of AML in an attempt to define entities that are biologically homogeneous and that have prognostic and therapeutic relevance. Each criterion has prognostic and treatment implications but, for practical purposes, antileukemic therapy is similar for all subtypes.

Since myelosuppression is an anticipated consequence of both the leukemia and its treatment with chemotherapy, patients must be closely monitored during therapy. Facilities must be available for hematologic support with multiple blood fractions including platelet transfusions, as well as for the treatment of related infectious complications. Randomized trials have shown similar outcomes for patients who received prophylactic platelet transfusions at a level of $10,000/\text{mm}^3$ rather than $20,000/\text{mm}^3$. The incidence of platelet alloimmunization was similar among groups randomly assigned to receive pooled platelet concentrates from random donors; filtered, pooled platelet concentrates from random donors; ultraviolet B-irradiated, pooled platelet concentrates from random donors; or filtered platelets obtained by apheresis from single random donors. Colony-stimulating factors – e.g., granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF) – have been studied in an effort to shorten the period of granulocytopenia associated with leukemia treatment. If used, these agents are administered after completion of induction therapy. GM-CSF was shown to improve survival in a randomized trial of AML in patients aged 55 to 70 years (median survival was 10.6 months versus 4.8 months). In this trial, patients were randomized to receive GM-CSF or placebo following demonstration of leukemic clearance of the bone marrow; however, GM-CSF did not show benefit in a separate similar randomized trial in patients aged 60 years and older. In the latter study, clearance of the marrow was not required before initiating cytokine therapy. In a randomized trial of G-CSF given following induction therapy to patients older than 65 years, complete response was higher in patients who received G-CSF, due to a decreased incidence of primary leukemic resistance. Growth factor administration did not impact on mortality or on survival.

Cytogenetic analysis provides some of the strongest prognostic information available, predicting outcome of both remission induction and post-remission therapy. Cytogenetic abnormalities that indicate a good prognosis include $t(8;21)$, $inv(16)$, and $t(15;17)$. Normal cytogenetics portend average-risk AML. Patients with AML that is characterized by deletions of the long arms or monosomies of chromosomes 5 or 7; by translocations or inversions of chromosome 3, $t(6;9)$, $t(9;22)$; or by abnormalities of chromosome 11q23 have particularly poor prognoses with chemotherapy. These cytogenetic subgroups predict clinical outcome in elderly patients with AML as well as in younger patients. The fusion genes formed in $t(8;21)$ and $inv(16)$ can be detected by reverse-transcriptase polymerase chain reaction (RT-PCR), which will indicate the presence of these genetic alterations in some patients in whom standard cytogenetics was technically inadequate. RT-PCR does not appear to identify significant numbers of patients with good risk fusion genes who have normal cytogenetics.

RECURRENT AML

There are a number of agents with activity in recurrent AML. A study with mitoxantrone and cytarabine was successful in 50% to 60% of patients who experienced relapse after initially obtaining a complete remission. Other studies using idarubicin and cytarabine or high-dose etoposide and cyclophosphamide reported similar results.

The immunotoxin *gemtuzumab ozogamicin* has been reported to have a 30% response rate in patients with relapsed AML expressing CD33. This included 16% of patients who achieved complete responses and 13% who achieved a CRp, a new response criteria defined for this trial. CRp refers to clearance of leukemic blasts from the marrow, with adequate myeloid and erythroid recovery but with incomplete platelet recovery (although platelet transfusion independence for at least one (1) week was required). It is not clear whether the inadequate platelet recovery is due to megakaryocyte toxic effects of *gemtuzumab* or to subclinical residual leukemia. The long-term outcomes of patients who achieve CRp following *gemtuzumab* are not yet known. *Gemtuzumab* induces profound bone marrow aplasia similar to leukemia induction chemotherapy and also has substantial hepatic toxic effects, including hepatic venoocclusive disease.

The farnesyltransferase inhibitor R115777 demonstrated a 32% response rate in a Phase I study in patients with relapsed and refractory acute leukemia (two complete responses and six partial responses in 24 patients treated) and has entered Phase II trials. A subset of relapsed patients treated aggressively may have extended disease-free survival; however, cures in patients following a relapse are thought to be more commonly achieved using bone marrow transplantation. A retrospective study from the International Bone Marrow Transplant Registry compared adults younger than 50 years with AML in second complete remission who received HLA-matched sibling transplantation versus a variety of consolidation approaches.

The chemotherapy approaches were heterogeneous; some patients received no consolidation therapy. The transplantation regimens were similarly diverse. Leukemia-free survival appeared to be superior for patients receiving bone marrow transplants for two groups: Patients older than 30 years whose first remission was less than one (1) year; and patients younger than 30 years whose first remission was longer than one (1) year. Allogeneic bone marrow transplantation in early first relapse or in second complete remission provides a disease-free survival rate of approximately 30%. Therefore, some investigators advocate allogeneic bone marrow transplantation in early first relapse to avoid the toxic effect of reinduction chemotherapy. Allogeneic bone marrow transplantation can salvage some patients whose disease fails to go into remission with intensive chemotherapy. Autologous bone marrow transplantation is a reasonable option for patients in second complete remission, offering a disease-free survival that may be comparable to autografting in first complete remission.

Arsenic trioxide, an agent with both differentiation-inducing and apoptosis-inducing properties against acute promyelocytic leukemia (APL) cells, has a high rate of successful remission induction in patients with relapsed APL.

Clinical complete remissions have been reported in 85% of patients induced with arsenic trioxide, with a median time to clinical complete remission of 59 days. Eighty-six percent of evaluable patients tested negative for the presence of PML-RAR α transcript after induction or consolidation with arsenic trioxide. Actuarial 18-month relapse-free survival was 56%. Induction with arsenic trioxide may be complicated by APL differentiation syndrome (identical to ATRA syndrome), prolongation of QT interval, and neuropathy.

INCIDENCE OF AML

A review of available tracking databases was performed to evaluate the number of patients with leukemia and AML by geographic region. The estimates for all leukemias are presented below.

The distribution of AML within the total leukemic population is ~32% (SEER statistics).

*Incidence/Prevalence/Mortality of Leukemia*¹

Region (000)	Incidence	Mortality	1-Year Prevalence	5-Year Prevalence
Eastern Europe	21.5	17.0	14.3	46.5
Northern Europe	10.2	6.5	6.5	20.8
Southern Europe	14.1	11.0	9.1	30.6
Western Europe	19.7	15.2	13.9	24.7
U.S.	21.4	16.3	13.0	62.7

From these estimates, we can predict the potential AML populations for these regions. These data are presented in the following tables.

Incidence of AML and Estimated Population for Study

Region (000)	Incidence	Initial CR	CR < 12 mo.	CR > 12 mo.
Eastern Europe	6.9	4.5	2.9	1.6
Northern Europe	3.3	2.1	1.4	0.8
Southern Europe	4.5	2.9	1.9	1.1
Western Europe	6.3	4.1	2.6	1.5
U.S.	6.8	4.5	2.8	1.6

FIRST RELAPSE REVIEW

Historic Response Estimates and Accrual

Response and survival rates in recurrent AML are dependant on a variety of patient specific factors. These include duration of the prior response, a prior response, patient age, cytogenetics of disease (surrogate for duration of response). A review of the literature is presented below evaluation these outcome variables from a historic perspective.

¹ Globocan/SEER databases

Response Rate by Prior CR Duration

Study	1st CR < 12 mo			1st CR > 12 mo		
	N	% CR	CI	n	%CR	CI
Rees ²	251	13	(8-18)	234	48	(42-55)
Keating ³	105	19	(12-28)	82	62	(51-73)
Thalhammer ⁴	121	33	(25-42)	47	55	(40-70)
Hiddermann ⁵	87	46	(35-57)	49	60	(44-73)

Response Rate by Age

Author	Age < 60			Age > 60		
	N	% CR	CI	n	%CR	CI
Rees	375	33	(26-38)	110	19	(2-28)
Keating	208	36	(29-42)	35	14	(5-30)
Hiddermann	104	54	(44-64)	32	44	(26-62)

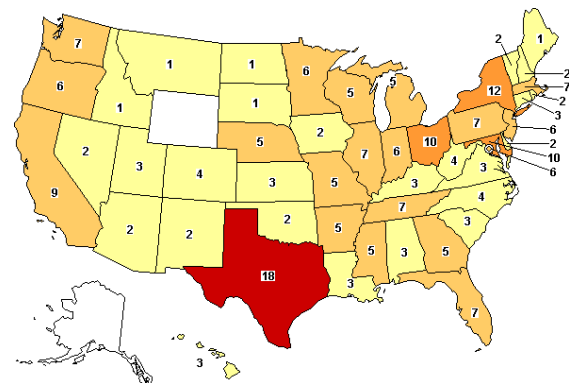
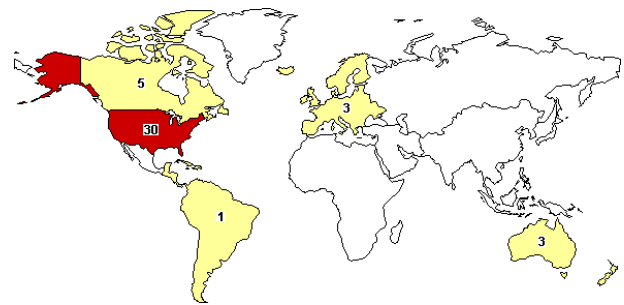
As can be seen, response rate is related to both age > 60 and prior response history. Overall, about 36% of the patients from non-stratified studies present with a history of durable CR > 12 months. Likewise, about 21% of patients present over age 60. The weighted CR rates for these studies are ~23% for patients with a prior response < 12 months and ~53% for patients with a prior response > 12 months. The weighted average based on age demonstrates that patients < 60 experience a CR rate of ~37% while patients > 60 have CR rates of ~22%.

FOCUSED STUDY LOCATIONS

The incidence of AML is comparatively low. As a result, center selection and geographic locations will impact the accrual of the study and the eventual times. In addition, other competitive studies may impact enrollment.

Below are maps indicating studies underway for the treatment of relapsed AML in the U.S. and ex-Eastern Europe. These data, coupled with the incidence data and site surveys, indicate that sites in Eastern Europe will provide extremely ideal candidates for enrollment. Estimates from Ockham surveys indicate that Eastern European sites will see about 30 patients a year eligible and will screen in about 12 per year. These estimates are much higher than the 0.32 patient/site/month historic enrollment rates.

² Rees Lancet 1986;236:1236
³ Keating MJ JCO 1989; 7: 1071
⁴ Thalhammer F Ann Hem 1996; 72: 216
⁵ Hiddermann W Leukemia 1990; 4: 184



PRIOR REGULATORY RIGOR

Ockham reviewed prior U.S. Food and Drug Administration (FDA) approvals for compilation of this synopsis.

FDA Written Agreements

The use of endpoints, scoring systems, diagnostic categorization, and other design-specific issues may best be captured in writing from the FDA. The Omnibus Budget Reconciliation Act (OBRA) allows for enforcement of written agreements with FDA should a dispute arise during the NDA process or during the advisory committee meetings. Cases of agreement (or lack of dissent) by agency officials (either by omission or verbally) not being recognized by the advisory committee have occurred. This becomes important when standards of practice or diagnostic classification change from the start to the end of the registration trial. In many cases, the committee will want to hold the older protocol to the current standard.

Advisory Committee Acceptance

In many cases, a request for a current advisory committee member to be present to hear and comment on pre-pivotal discussions can be arranged. This may help address the acceptance of the design from a clinical practice standard as well as the traditional regulatory rigor that the agency applies.

International Working Group Guidelines

The American Society of Clinical Oncology (ASCO) published (January 2004) International Working Group guidelines for AML. Although the guidelines are not mandatory, care should be given to their impact on peer-reviewed outcomes data five (5) years from now. The general acceptance of key areas

should be anticipated over the five years. This is not dissimilar to changes in Non-Hodgkin's Lymphoma classification and staging observed in recent years.

These include:

- WHO diagnostic criteria
- Flow cytometry and cytogenetics
- The variety of CR classifications.

EMEA Orphan Designation

The European Medicines Agency (EMA) orphan designation differs slightly from that in the U.S.

If orphan designation is desired in Europe, consideration for filing should be made as therapeutic indication rather than agents are given this designation. Once the therapeutic indication is covered, another product in the therapeutic indication can not receive the designation.