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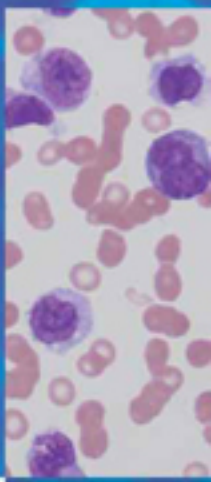
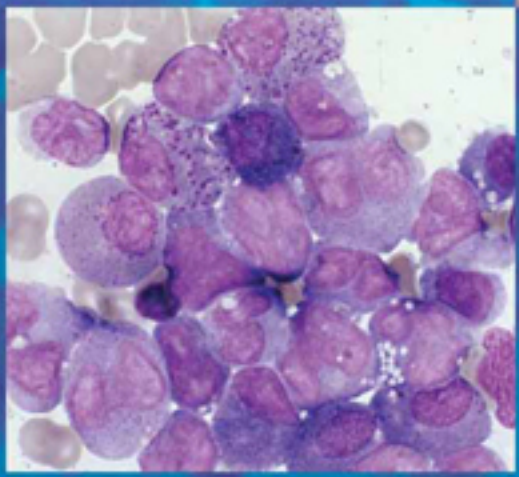
Acute Leukemias





HEMATOLOGIC MALIGNANCIES

Springer

E.H. Estey · S.H. Faderl · H.M. Kantarjian

Hematologic Malignancies: Acute Leukemias

With 44 Figures and 51 Tables

Springer

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Part I – Acute Myeloid Leukemia

Therapy of AML

Elihu Estey

Contents

1.1 Introduction

As with any disease, there are three general options for treatment of AML: supportive care only, standard therapy, and investigational therapy. Although, as discussed below, there are instances where the first option is preferable, the natural history of AML typically mitigates against it [1]. Since by definition there is much more information available about standard than about investigational therapy, most patients prefer the former, provided outcome with it is satisfactory. Hence, this review will begin by describing standard therapy, with emphasis on the factors that predict success following its use. Subsequent discussion will focus on investigational options of potential use for patients in whom results with standard therapy are poor.

The criteria for a diagnosis of AML have changed with publication of a report sponsored by the WHO [2]. Previous criteria were those of the FAB group and required a minimum of ≥30% blasts [3]. The WHO has lowered this to ≥20% blasts, in the process eliminating the myelodysplastic syndrome refractory anemia with excess blasts in transformation (RAEB-t). Although data mentioned below suggest that blast counts between 10–100% are not themselves independent predictors of outcome, we will adhere to the WHO criterion in the material that follows.

1.2 Standard Therapy

1.2.1 "3+7"

Standard therapy consists of "induction" and "postremission" phases. The intent of the former is to produce, and of the latter to prolong, a complete remission (CR) defined as a marrow with <5% blasts and peripheral blood with >1000 neutrophils and >100 000 platelets. The importance of CR relates to its ability to prolong survival. Thus, 40 years ago, Freireich et al. [1] documented that patients who achieved CR lived longer than those who did not. The difference in survival time was entirely due to the time spent in CR, suggesting that this difference resulted from achievement of CR rather than from a superior natural history. The risk of relapse from CR is constant for the first 2 years, but once patients have been in CR for 3 years it declines precipitously (to <10%), allowing such patients to be considered potentially cured [4].

For 30 years most patients with AML who have been treated have received remission induction therapy with what is commonly called "3+7." The "3" refers to the 3 days on which patients receive an agent (most commonly an anthracycline such as daunorubicin or idarubicin) that affects topoisomerase II and the "7" to the 7 days of cytosine arabinoside (ara-C) that accompany and follow the anthracycline. If blasts remain in a marrow aspirated 14 days after beginning therapy (day 14), a second course is often administered, with the number of days of anthracycline reduced to 2 and of ara-C to 5. If the day-14 marrow contains very few blasts, the marrow is reaspirated weekly until response (CR or reappearance of blasts) becomes clear.

Upon documentation of CR, patients frequently receive additional courses of anthracycline + ara-C, with a reduction in the doses or in the number of doses. While some such therapy is almost certainly necessary today, the proper amount likely depends on the intensity of the first several courses. For example, a German AML Cooperative Group (AMLCG) trial randomly assigning patients who had received 1 post-CR course to no further therapy or 3 years of maintenance found that the latter prolonged relapse-free survival time (RFS) from 7% to 30% [5]. However, a subsequent randomized AMLCG trial found much less improvement in RFS (28% vs. 35% at 3 years) and no difference in survival when patients in the no-further-therapy group received a more intense induction regimen and one intense postremission course [6]. Regarding the specific number of postremission courses to administer following a first course of 3+7, the British NCRI (formerly MRC) group found no difference between 4 and 7 courses [7].

1.2.2 Outcome Following 3+7

CR, survival, event-free survival, and relapse-free survival rates are very variable after administration of 3+7; substantial numbers of patients die within a few weeks of beginning therapy and substantial numbers are potentially cured. Thus, speaking of an average outcome is not particularly informative. As with all anti-AML therapy, two general types of variables are associated with outcome: those that predict treatment-related death before response to induction therapy can be evaluated ("TRD") and those that predict true resistance to therapy. The criterion for "early death" is somewhat arbitrary. Very few patients achieve CR before day 21. Thus, deaths before day 21 are true early deaths resulting from supportive care failure. However, half the patients who will achieve CR have done so by day 35. Accordingly, failure in patients who die between days 21 and 35 and who have not achieved CR is due to both failure of supportive care and resistance. Beyond day 35, resistance to therapy becomes increasingly responsible for failure to enter CR. In CR, treatment-related mortality is rare (5–10%) in contrast to relapse from CR (50–100%).

1.2.3 Predictors of TRD

The principal predictor of TRD is pretreatment performance status. Table 1.1 illustrates that the proportion of patients who are bed-ridden most (performance sta-

Table 1.1. Effect of performance status and age on treatment-related death (TRD) rates

Age	Performance status (Zubrod)	Patients	Dead by day 21	Dead by day 35
<50	<3	490	3%	5%
<50	>2	37	32%	46%
50–59	<3	361	4%	7%
50–59	>2	28	25%	38%
60–69	<3	372	7%	11%
60–69	>2	45	43%	50%
70–79	<3	328	8%	17%
70–79	>2	46	52%	68%
80	<2	60	16%	26%
80	>2	10	40%	70%

tus 3), or all (performance status 4) of the time increases with increasing age. However, performance status is more important than age. Thus, while the proportion of patients dead 5 weeks after beginning treatment rises from 5% to 26% as age increases from <50 to ≥80, patients with performance status 3–4 but who are below age 50 have higher TRD rates than more ambulatory patients age ≥80.

Renal and hepatic function may also be more useful in predicting TRD than age. For example, in patients with performance status <2 and calling a bilirubin or creatinine >1.9 abnormal, TRD rates within 35 days of beginning treatment were 5% (43/808), 21% (7/34), 13% (91/688), and 36% (21/58) among, respectively, patients age <60 with normal pretreatment bilirubin and creatinine, patients age <60 with abnormal bilirubin or creatinine, patients age >59 with normal bilirubin and creatinine, and patients age >59 with abnormal bilirubin or creatinine. The ability of various "comorbidity" scales to predict TRD independent of performance status, age, and organ function is also being evaluated [8, 9].

1.2.4 Cytogenetics as the Principal Predictor of Resistance in AML

For many years cytogenetic findings in AML blasts have been the principal predictor of relapse from CR, or failure to achieve CR despite living long enough (e.g., >35 days) to plausibly have done so [10–12]. Three groups can be distinguished. A *better-prognosis* group consists of patients with a pericentric inversion of chromosome 16 [inv 16] or a translocation (t) between chromosomes 8 and 21 (t 8;21); less often there is a t(16;16). Each of these abnormalities disrupts the function of a transcription factor ("core binding factor," CBF) regulating the expression of genes important in hematopoietic differentiation [13]. At most 10% of unselected patients have CBF AML; these patients are typically age <60. A *worse-prognosis* group includes patients with monosomies, or deletions of the long arms, of chromosomes 5 and/or 7 typically accompanied by several additional chromosome abnormalities. Patients with such "–5/–7 AML" constitute 30–40% of all patients, are usually older (>50–60), and disproportionately have "secondary AML," i.e., a history of abnormal blood counts for ≥1 month before the diagnosis of AML ("antecedent hematologic disorder", AHD) or have received alkylating agents for other conditions, e.g., breast or ovarian cancer or lymphoma. Some consider the rare patients with inv (3)/t (3;3), t(6;9), t(6;11), t(11;19) or >3 abnormalities without –5/–7 to belong to the worse prognosis group. The remaining 50–60% of patients primarily consist of the 35–40% of all patients with a normal karyotype; these patients comprise an *"intermediate" prognosis group*, whose prognosis bears more resemblance to the worse- than the better-prognosis group.

1.2.5 Effect of Higher Doses of Ara-C

The significance of cytogenetics applies not only to patients given 3+7 but also to patients given higher doses of ara-C, e.g., 0.4–3 g/m²/dose; the 0.4–1.5 g/m² dose is often called "intermediate-dose ara-C" (IDAC); doses in the 2–3 g/m2 range are known as "high-dose ara-C ("HDAC)"); in particular, the benefit obtained with IDAC/HDAC is proportional to sensitivity to the "standard" doses used in 3+7 (100–200 mg/m² daily ×7). In a seminal study randomizing patients in CR among different doses of ara-C [14], Cancer and Leukemia Group B (CALGB) showed that HDAC's biggest impact was in

CBF AML where it produced average cure rates in excess of 50%. In the normal karyotype group, IDAC and HDAC were equivalent, with each superior to standard doses, i.e., those in 3+7. In the worse-prognosis group any differences among HDAC, IDAC, and standard doses were small relative to the poor outcome observed with all three doses. NCRI data suggest that similar results can be obtained in CBF AML with IDAC as with HDAC [10], leading to an NCRI trial randomizing between these 2 doses.

1.2.6 Beyond Cytogenetics

Although cytogenetic findings remain the most important prognostic factor in AML, there is considerable variability in outcome particularly within the intermediate and favorable groups. The presence of (a) secondary AML, (b) "white blood cell index," (c) "secondary" chromosome abnormalities superimposed on the primary abnormalities noted above, and (d) molecular abnormalities such as gene mutations and deregulated gene expression are useful in unravelling this heterogeneity. The poorer outcome in secondary rather than in de novo AML is well known and appears independent of the association between secondary AML and worse-prognosis cytogenetics [15]. Nguyen et al. for the French AML Intergroup found that relapse-free survival in patients with t (8;21) given IDAC (or an allogeneic transplant) varied as a function of a "white blood cell index" defined as [WBC×% marrow blasts]/100 [16]. Long-term RFS was >75% with an index <2.5, 60% with an index 2.5–20, and 30% with an index >20. In general, the presence of secondary chromosome abnormalities has little affect on prognosis. However, the German AML Intergroup and Cancer and Leukemia Group B (CALGB) have shown that trisomy 22 improves relapse-free survival in inv [16] AML [17, 18], while the German group has also shown that a missing Y chromosome is associated with shorter survival t(8;21) [17]. Of more general interest, mutations in receptor tyrosine kinases (RTK), such as *KIT,* and in RAS genes have been found in 25% of cases of inv 16 AML and in 10% of cases of t(8;21) AML; *KIT* mutations appear associated with an inferior prognosis [19–22].

Given its frequency, the normal karyotype group is the one in which prognostic heterogeneity is most problematic. Such patients often have molecular abnormalities involving *FLT3*, *NPM1*, *CEBPA*, *MLL*, *RAS*, *BAALC*, or *EVI,1*. Internal tandem duplications (ITD) within the juxtamembrane domain of the RTK *FLT3* occur in 28–34% of patients with normal karyotype AML and are consistently associated with a significantly inferior outcome [23–27]. An additional 10–15% of these patients have mutations within the activation loop of the second tyrosine kinase domain (TKD) [25, 26, 28, 29]. A recent meta-analysis suggests that *FLT3* TKD mutations also negatively affect RFS, although the British NCRI group has recently reported a favorable effect [30, 31]. The most common somatic gene alterations in AML are mutations in the nucleophosmin (*NPM1*) gene, resulting in cytoplasmic rather than nuclear localization of the *NPM1* protein. *NPM1* mutations have been reported in 48–64% of normal karyotype AML [32–36]. Recent studies have found that overall survival (OS) and relapse-free survival (RFS) are significantly better in *NPM1*+/*FLT3* ITD– patients contrasted with *NPM1*– and *NPM1*+/*FLT3* ITD + patients [32–36]. *NRAS*/*KRAS* mutations occur in approximately 18% of normal karyotype AML [37]. Although no consistent prognostic effect has yet been shown, there may be such an effect after accounting for mutations in other genes, such as dominant negative mutations in the transcription factor *CEBPA* and partial tandem duplications (PTD) in the *MLL1* gene, which occur in 15–18% and 8–11% of normal karyotype cases, respectively. *CEBPA* mutations are associated with superior OS and RFS [38–40], while *MLL1* mutations predict for inferior RFS without significant effect on OS [41–44]. A significant negative prognostic effect on these two outcomes has also been reported in cases with aberrant overexpression of *BAALC*, a gene that is physiologically expressed in brain tissue and in hematopoietic progenitor cells [45, 46].

Genome-wide gene expression profiling based on DNA microarrays has provided additional prognostic information [47–49]. In particular, hierarchical clustering has identified two normal karyotype-predominant classes that differed in OS, and a gene expression predictor emerged as the strongest prognostic factor in multivariate analysis. These findings have been validated prospectively in an independent data set [50].

Table 1.2, based on outcome in younger adults given anthracycline + IDAC/HDAC, provides a prognostic system combining genetic and cytogenetic information. The value of cytogenetics in predicting RFS can also be enhanced by incorporating information regarding response to induction therapy [51].