

Therapy of AML

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	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 $\geq 30\%$ blasts [3]. The WHO has lowered this to $\geq 20\%$ 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	Perfor- mance status (Zubrod)	Pa- tients	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 $[WBC \times \% \text{ marrow blasts}] / 100$ [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 *EVI1*. 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].

Table 1.2. Approximate 3-year event-free survival probabilities based on cytogenetic and molecular findings in younger adults treated with anthracycline + IDAC/HDAC

Group	
EFS >75%	t(8;21) with WBC index <2.5 and without kit mutation inv(16), +22 and without kit mutation
EFS 50–75%	Other inv(16) without Kit mutation t(8;21) with WBC index 2.5–20 and without kit mutation Normal karyotype and CEBPA+ Normal karyotype and NPM1+/FLT3 ITD– del(9q)
EFS 25–50%	Inv 16 with kit mutation t(8;21) with WBC index >20 or with kit mutation t(9;11) Normal karyotype and NPM1–/FLT3 ITD– Normal karyotype and NPM1+ or –/FLT3 ITD+ Normal karyotype and MLL1 PTD+
EFS <20%	inv(3)/t(3;3) t(6;9) t(6;11), t(11;19) abn(12p) +8 +11 +13 +21 –5/–7 not as sole abnormality Complex karyotype

1.2.7 Effect of Allogeneic Stem Cell Transplant (Allo SCT)

Although first used in patients with chemotherapy-resistant AML, the most frequent use of allo SCT has been in patients in first CR. Controversy over whether such patients should receive an allo SCT rather than continue the therapy that produced CR has been unabated for 25 years. A disinterested observer might thus suspect that any differences between chemotherapy and allo SCT, as commonly practiced, must be relatively small.

Examination of the literature suggests that such is the case. Formal comparisons between allo SCT and chemotherapy in first CR typically find that the proportion of patients who do not receive allo SCT, although they have been assigned to the procedure because suitable donors exist, is higher than the proportion of patients without donors who do not receive chemotherapy [52, 53]. It is suspected that patients assigned to a treatment but who do not receive it have worse prognoses than patients who receive the treatment. To avoid such “selection bias,” comparisons involve patients with a donor, regardless whether the patients receive allo SCT, and patients without a donor. Such “biologically randomized” comparisons, after eliminating from analysis patients in the no-donor group who have an event in CR before the average patient with a donor is transplanted, typically find that the donor group has longer RFS (despite higher TRD rates) but similar OS [52–55]. Thus, while the rate of TRD + relapse is lower with allo SCT, patients in the no-donor group live longer once relapse has occurred.

In light of the prognostic heterogeneity of AML, it is important to assess whether particular groups do better with allo SCT, in particular patients with “poor prognosis” cytogenetic, or molecular, features, or younger patients (given the effect of age on TRD, which averages 20–25% after allo SCT). Slovak et al. [12] reported that relative risks of death in patients assigned chemotherapy rather than allo SCT were as follows: 2.04 if favorable cytogenetics, 0.70 if intermediate cytogenetics, and 1.82 if unfavorable cytogenetics. However, of relevance in the favorable and intermediate groups, patients assigned chemotherapy received only 1 course of IDAC/HDAC, and of relevance given the small sample sizes (each of the 95% confidence intervals included 1.00) the prognostic heterogeneity of each of the cytogenetic groups may have affected the conclusions. The paper of Burnett et al. [54] seems to address these criticisms given the authors’ use of a more intense chemotherapy regimen in their no donor group, and their use of a prognostic index that incorporated information about response to induction into their cytogenetic classification [51]. With sample sizes approximately three-fold greater than those of Slovak et al., they found that the only donor group that had superior OS was the intermediate prognosis group ($p=0.02$, 56% vs. 45% at 7 years). They noted that “in the absence of an overall survival benefit, this could be a chance subgroup effect, and it would not be valid to conclude that there was definite evidence of

benefit.” A donor–no donor comparison by Jourdan et al. [55] also found that only the intermediate prognosis donor group had superior OS ($p = 0.02$, 55% vs. 70% at 7 years), although the same comment about subgroup effect can be made, in addition to which only 79% in the no-donor group received ≥ 1 course of IDAC/HDAC, and the authors’ prognostic index incorporated WBC count and FAB category, neither commonly recognized as particularly “prognostic,” in addition to cytogenetics and response to the first course of treatment. Two groups have used a donor–no donor comparison to examine the effect of allo SCT in patients with poor prognosis molecular abnormalities. The NCRI found equivalent OS and RFS in patients with a FLT3 ITD [56] (68 donor, 114 no-donor patients), while examining patients who were *NPM1*– or *NPM1*+/*FLT3* ITD + the German-Austrian AML group reported longer RFS in the donor group ($p = 0.001$, e.g., 60% vs. 40% at 2 years) [33]; OS was not reported.

All the patients in the Jourdan et al. [55] paper were age < 45 , while those in the papers of Slovak et al. [12] and Burnett et al. [54] were age < 56 . Only the latter paper examined the effect of age, finding no difference in OS among patients aged 0–14, 15–34, or 35–56 according to whether they were in the donor or no-donor group. This finding, which contradicts prior belief that patients less than 20–30 years old should receive an allo SCT in first CR, resulted from improvements in chemotherapy (e.g., use of IDAC/HDAC). It is not implausible that similar improvements may eventually affect SCT. For example, TRD rates may be reduced by use of peripheral blood as the stem cell source or by using reduced-dose conditioning regimens (discussed in the section on investigational treatments), thus altering OS in favor of allo SCT. However, there are currently no data indicating that allo SCT prolongs OS in any patient in first CR; furthermore, allo SCT typically has more long-term complications than chemotherapy. If conventional allo SCT is performed, there seems to be no advantage to administer HDAC or other postremission therapy prior to transplantation.

While the donor–no donor comparison approach has obvious value, it tends to mask the value of allo SCT in patients who are fit enough to undergo the procedure. Thus, a transplant–no transplant comparison might also be of interest. Lending credence to performing this type analysis is the NCRI’s report that patients with a donor who were not transplanted had similar outcomes as patients without a donor [54]. Of course,

if the proportion of patients with a donor who receive allo SCT is sufficiently low, the transplant–no transplant comparison becomes primarily of academic interest. In this regard, it has been shown that even in relatively young patients the impact of allo SCT on the management of AML is quite small [57, 58].

1.2.8 Effect of Autologous Stem Cell Transplant (Auto SCT)

In several of the studies discussed above, patients in the no-donor group were randomized between chemotherapy and auto SCT in first CR. Comparisons of the latter two strategies may be confounded if, as in the NCRI trial, both groups get the same amount of chemotherapy, with the chemotherapy group then stopping treatment, but the auto SCT group then proceeding to auto SCT [59]. Typically studies report longer RFS with auto SCT, but have not found longer OS, either on average or in any subgroup [52, 53]. While there is little doubt that TRD rates with auto SCT will decline thus possibly tilting the OS balance in its favor vis a vis chemotherapy, it is also plausible that this balance might be shifted to favor chemotherapy if new non-SCT, such as those discussed below, reduce the risk of relapse.

1.2.9 Effect of Colony Stimulating Factors (CSFs)

As with auto SCT, the space devoted to a discussion of CSFs in a current review of treatment of AML is much less than would have been the case several years ago, reflecting a decreased interest in such therapy. CSFs and specifically G- and GM-CSF have neither decreased TRD (or serious morbidity) when administered during/after anthracycline + ara-C [60, 61] nor decreased resistance (e.g., by “priming” blasts to the effects of these drugs) when given before/during such therapy [62–64]. An exception was a trial [65] randomizing 640 patients aged 18–60 to receive or not receive G-CSF in conjunction with 2 courses of standard dose ara-C, the first with idarubicin and the second with amsacrine, whose mechanism of action is presumed similar to that of idarubicin. Idarubicin was given on days 6–8, rather than days 1–3 as in the usual 3+7 regimen, and amsacrine on days 4–6, rather than 1–3. The authors hypothesized that delayed administration would prevent interference of the “cell-cycle-dependent synergy” be-

tween G-CSF and ara-C. G-CSF did not affect outcome in unfavorable prognosis patients (defined to include those with secondary AML), but improved RFS in intermediate-prognosis patients (as defined by cytogenetics and de novo AML) at 4 years from 33 +/3% to 45 +/3%. There currently appear to be few large trials attempting to confirm this result; until then there is no reason to routinely use G- or GM-CSF. Rather, a 3- to 4-day trial of these CSFs might be tried in patients who have developed serious infections while still neutropenic after chemotherapy.

1.2.10 Candidates for “Standard” Therapy

As noted in the introductory paragraph, the fundamental principle underlying treatment of AML is to use the prognostic information illustrated in Tables 1.1, 1.2 to decide which patients are candidates for standard therapy. “Standard therapy” is defined here as therapy whose results are well known. It thus primarily consists of 3+7, of IDAC/HDAC +/- anthracycline, and of allo or auto SCT, as commonly administered, e.g., using cyclophosphamide and busulfan as the preparative regimen. In the following discussion we will focus on cytogenetics assuming that the molecular tests cited in Table 1.2 are routinely unavailable, but will include discussion as to how the latter might affect management. The general algorithm we will use is presented in Table 1.3. In principle, the best way to identify patients at low risk of TRD would almost certainly be via a predictive “model” that incorporates performance status, age, organ function, and various comorbidities [66]. Regretta-

bly however, age is often used alone as a surrogate for risk of TRD. Currently, the significance of this practice is reduced given that investigational drugs are unavailable for patients with poor performance status, abnormal organ function, or significant comorbidities. At any rate we will use ≥ 60 –65 as the age associated with an increased risk of TRD. It should be recognized however that each additional year of age beyond age 18 is associated with a poorer prognosis, i.e., any age cut-off is arbitrary [67].

1.2.10.1 Younger Patients (Age < 60) with CBF AML

These patients should receive IDAC or HDAC. This recommendation is supported by the CALGB trial described in the section on IDAC/HDAC. There are conflicting data regarding whether, once HDAC is given (with an anthracycline) during induction, further HDAC is of value during postremission therapy. A SWOG trial suggested “yes” [68], an Australasian Leukemia and Lymphoma Group trial suggested “no” [69]. Patients with CBF AML were a minority in both studies’ patients; the Australasian, but not the SWOG, study administered etoposide in addition to idarubicin and ara-C. While it is thus difficult to fault a practice administering IDAC/HDAC only as part of postremission therapy, the author believes that the potential benefit from giving IDAC/HDAC during both induction and postremission phases is sufficiently high to justify this practice in patients whose risk of TRD is extremely low, e.g., performance status 1, age < 50. Retrospective surveys by CALGB suggest that 3–4 consecutive postremission cycles of HDAC (cumulative dose: 54–72 g/m²) are superior to one cycle (18 g/m²) [70, 71]. However, since the patients given only 1 cycle did not receive any other ara-C in remission, the CALGB results speak primarily to the effectiveness of ara-C rather than to value of 3 or 4 postremission cycles of HDAC. Indeed, results of the German AML Intergroup survey [17] suggest that two cycles of HDAC – in combination with an anthracycline or mitoxantrone – are equally effective as 3 or 4, and that there is no prognostic impact of HDAC on RFS in a dose range between 20.8 g/m² and 56.8 g/m². Furthermore, use of only 1 cycle of HDAC consolidation in the British AML10 study [10] produced results in patients with CBF AML similar to those seen with 3 or 4 postremission courses in the CALGB studies.

Table 1.3. General approach to management of AML

Probability of TRD	Probability of resistant AML	Therapy
Low	Low	Standard, including IDAC or HDAC
Low	High	Investigational (high intensity)
High	Low	Standard without IDAC/HDAC
High	High	Investigational (low intensity)

Nonetheless, for reasons similar to those explaining his preference for IDAC/HDAC during both induction and postremission therapy, the author would favor administration of 3 or 4 postremission cycles. Neither allo SCT nor auto SCT should be used in the average CBF patient in first CR.

CBF patients with KIT mutations and t(8;21) patients with WBC index >20 have much less favorable outcomes than other patients with similar cytogenetics [19–22] (Table 1.2). Such “poor-prognosis” CBF patients might be candidates for investigational therapy provided large elements of the standard therapy described above are retained in deference to the 25–50% success rate even in such poor-prognosis patients. For example, a tyrosine kinase inhibitor might be added in patients with KIT mutations.

Other candidates for standard therapy are those age <60 (low risk of TRD) with a normal karyotype who have either a CEBPA mutation or have an NPM mutation and have wild-type FLT3 (50–75% success rate, Table 1.2). Given the low-risk of TRD, the author favors use of IDAC/HDAC with anthracycline during both induction and postremission phases.

1.2.11 Candidates for Investigational Therapy

1.2.11.1 Elderly Patients (Age ≥60–65)

Table 1.4 presents results of trials investigating standard therapy in elderly patients. The depicted average median survival times of 10 months make it difficult to recommend standard therapy to many such patients. This is particularly so given the 15–20% risk of TRD occurring during the approximately 1–2 month remission induction period (Table 1.4), noting that some of the trials shown in Table 1.4 limited eligibility to patients with better performance status, normal organ function, and no major infection. Reducing the doses/duration of anthracycline and/or cytarabine has decreased both early mortality and the anti-AML efficacy of treatment, resulting in no improvement in survival [76]. Addition of G-CSF or GM-CSF to an anthracycline + ara-C, substitution of mitoxantrone for an anthracycline, or use of single agent gemtuzumab ozogamycin [77] have also failed to lengthen survival (Table 1.4).

It is useful to attempt to identify groups of older patients for whom standard therapy might be reasonable. Two such groups are patients CBF AML and patients with a normal karyotype, who are age 60–69, have de novo AML, a Zubrod performance status 0–2, normal

Table 1.4. Outcomes in older patients given anthracycline + Ara-C

Study [reference]	Patients	Median survival	Probability survival at 2 years	CR rate	Induction death rate	Comment
ECOG [72]	234, age ≥56	7–8 months	≈ 20%	41%	19%	Results same with daunorubicin, idarubicin, or mitoxantrone and +/- GM-CSF priming
NCRI (formerly MRC), (AML 11) [7]	1314, age ≥56	≈ 12 months	≈ 25%	62%	16%	Results same with 1 or 4 courses post-CR and +/- G-CSF starting 8 days after end induction
SWOG [73]	161, age ≥56	9 months	19%	43%	15%	Survival worse with mitoxantrone + etoposide
HOVON [74]	211, age ≥60	≈ 10 months	≈ 25%	48%	15%	Results same +/- PSC-833
M.D. Anderson [75]	31, age ≥65	≥12 months	≈ 20%	48%	Not given	Ara-C at 1.5 g/m ² daily ×3; survival worse with single agent gemtuzumab

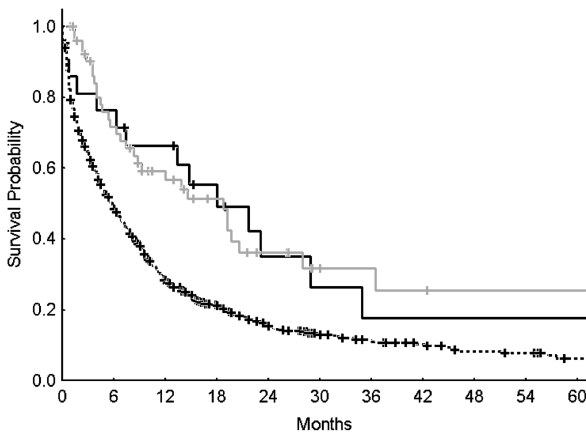


Fig. 1.1. Survival probabilities in three groups of elderly patients. *Black line* denotes patients with inv(16) or t(8;21) (n=22), *gray line* denotes patients with a normal karyotype and de novo AML who were age 60–69 with a good performance status, normal pretreatment organ function, and no pretreatment infection (n=54), while *dashed line* denotes other patients (n=627). The differences between the first two groups, on the one hand, and the third group, on the other ($p < 0.001$), suggest that while standard therapy might be appropriate for the first two groups, it is not for the third group.

values for bilirubin and creatinine, and no pretreatment infection. Both groups had a median survival of 18 months following various cytarabine-containing regimens, as given at M.D. Anderson Hospital (MDA), with only a 5–10% TRD rate (Fig. 1.1). However, the probabilities of being in CR 3 years after initial diagnosis, corresponding to the time when patients can be considered “potentially cured” ranged between 9% and 16%. Given these data, some patients might prefer standard, and other patients investigational, therapy.

The “favorable” elderly patients described above constituted only 8% of the 968 patients age 60 and above given induction therapy at MDA over the past decade. The others had a median survival, when given cytarabine- or anthracycline-containing therapy, of 6 months (Fig. 1.1), with a 6% probability of being in CR at 3 years, and a 25% TRD rate. Thus, I recommend new therapies for the great majority of older patients with untreated AML. The National Comprehensive Cancer Network, a consortium of prominent American cancer centers explicitly cites “clinical trial” as the preferred option in patients with untreated AML age 60 and above [78]. There is of course no assurance that results with investigational therapy will not be worse than those with 3+7. For example, a CALGB study in older patients

was stopped before accrual was completed because patients randomized to the investigational arm (daunorubicin + cytarabine + etoposide + PSC-833) had a higher death rate than patients randomized to the same 3 drugs without PSC-833 [79]. While investigational therapy may thus prove worse than standard, it seems fair to ask: “how much worse than 3+7 can an investigational therapy be.” The weight given to the recommendation for investigational therapy should increase as the number of unfavorable prognostic factors (age > 69, adverse cytogenetics, secondary AML, poor performance status, infection, abnormal organ function) increases (see also Table 1.2).

Any discussion of choice of therapy must refer to Sekeres et al.’s observations [80] that 74% of older patients estimated that their chances of cure with 3+7 were at least 50%; in contrast, 85% of their physicians estimated this chance to be <10%. While the most plausible cause of this discrepancy is patients’ natural tendency to believe what they want to believe, there may also be gaps in communication between physicians and patients.

1.2.11.2 Younger Patients (Age < 60) with Chromosome Abnormalities Other Than inv (16) or t(8;21)

Given their median age of 45, these patients would have a very considerable life expectancy if they did not have AML. Hence potential cure is of more significance for them than for older patients (age > 60), whose median age is 70. Figure 1.2 (top) indicates that the probability of being in CR 3 years after starting initial IDAC/HDAC-containing treatment (corresponding to our criterion for potential cure) in the most favorable subset of younger patients with $-5/-7$ (i.e., patients with de novo AML and a performance status < 3) is 10%. Their median event-free survival is 39 weeks (Fig. 1.2, bottom). Hence the author believes that investigational treatment should be the preferred option in younger patients with $-5/-7$, recalling that the weight of evidence suggests that these patients are not materially benefited by allo or auto SCT, as typically performed. Exceptions might be made for the rare patients who have $-5/-7$ as a single abnormality [81].

Younger patients with performance status < 3, de novo AML and other cytogenetic abnormalities (excluding inv 16 and t(8;21) have 3-year EFS that while statistically different than those in comparable $-5/-7$ patients

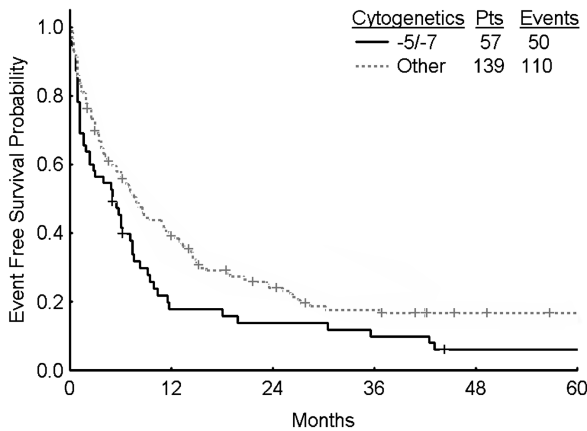


Fig. 1.2. Event-free survival probabilities following IDAC- or HDAC-containing regimens in patients age <60 with performance status <2 and with de novo AML (M.D. Anderson data 1991–2005). Despite these “favorable” features, outcome (particularly EFS at 3 years) in patients with “-5/-7” is such that investigational therapies are the preferred option. Although outcome is somewhat better in patients with other cytogenetic abnormalities (inv 16 and t(8;21) excluded) ($p=0.02$ for both EFS and OS), there is sufficient qualitative similarity between the two groups that the investigational therapy is also the preferred option in the other cytogenetic abnormality group.

are not materially different (e.g., 17% EFS at 3 years; Fig. 1.2 top). Hence, despite their median event-free survival of 74 weeks (Fig. 1.2), I believe that the preferred option in these patients is also investigational therapy. Obviously some would disagree with what is essentially a subjective view and believe that these patients are candidates for standard as well as investigational treatment. It is noteworthy however that phase 2 studies of new drugs are routinely performed in untreated patients with pancreas, or metastatic lung cancer, diseases in which median event-free survival is not materially different than the 74-week figure noted here.

1.2.12 Candidates for Either Standard or Investigational Therapy

1.2.12.1 Younger Patients with a Normal Karyotype

M.D. Anderson data (326 patients treated since 1990 with IDAC/HDAC-containing therapy) indicate that these patients have a 3-year event-free survival probability of 26%. It is not implausible that some patients when given this information would choose standard therapy,

assuming correctly that investigational therapy could be worse. Certainly given the reasonable success rate observed with standard therapy, investigational therapy in these patients should be based on standard therapy, a constraint that is less applicable for the patients described above in whom investigational therapy is the preferred option, particularly elderly patients and those young patients with -5/-7. In light of the relatively low risk of TRD, and the CALGB data suggesting the superiority of IDAC to standard doses of ara-C [14], IDAC should be included in either induction or postremission phases or both.

Young patients with a normal karyotype are a group for whom the molecular information outlined in Table 1.2 will be particularly important. For example, the presence of a FLT3 ITD would weigh the choice toward investigational therapy, while an NPM or CEBA mutation would favor the standard therapy option.

1.2.13 When Should Therapy Start?

At least several days are needed for results of cytogenetic and molecular studies to become available. However, patients with high (>100 000) or rapidly rising WBC counts or a somewhat lower count (>10 000–20 000) and symptoms of lung or brain involvement require immediate institution of definitive therapy, which should not be delayed by leukapheresis or use of hydroxyurea. However, in other patients delaying therapy to await cytogenetic and molecular results may be feasible. Knowledge of such results prior to beginning induction therapy is less important in younger patients since the risk of TRD is low, and investigational therapy could be given when results of induction therapy, and of cytogenetic/molecular tests, are known. However, initiation of investigational therapy only in CR is not optimal since it is known that the type of therapy used for induction has a powerful influence on outcome in CR (see, for example, [82, 83]). Older patients have higher rates of TRD, and hence the desirability of delaying a therapy that is unlikely to be successful (e.g., if the patient has -5/-7) is even greater. Older patients usually do not present with features demanding immediate therapy, making it possible to delay therapy for cytogenetic results. Among 197 patients presenting to MDA with WBC <50 000, multivariate analysis indicated that age and unfavorable cytogenetics were independent predictors of CR, but that days from MDA diagnosis to start

of treatment (delay) was not [84]. A delay of >9 days occurred in only 25% of patients. However, since 2000, survival is equivalent in the 49 patients age ≥ 60 beginning treatment >1 month from MDA diagnosis and in the 560 similarly aged patients beginning treatment sooner. Although selection bias may influence these findings, which are in contrast to those reported by the ECOG [72], they suggest that the risk of waiting to obtain results that might influence choice of therapy is less than the risk of giving therapy that is unlikely to be successful and may, as with 3+7 in older patients, be associated with significant rates of TRD. Furthermore, both the ECOG and MDA studies undoubtedly underestimate the interval from diagnosis to treatment since neither account for the interval from diagnosis by referring physicians to confirmation of diagnosis at the tertiary center.

1.2.14 Patients for Whom Investigational Therapy is Unavailable

It is important to recognize that, for logistical or financial reasons, investigational therapies are unavailable for many patients. The major group for whom ability to access new drugs is problematic are patients at high risk of TRD, e.g., older patients and patients with performance status 3–4. The options for these patients are 3+7, low-dose ara-C (LDAC, e.g., 20 mg bid \times 10–14 days by subcutaneous injection every 4–6 weeks), or “supportive care.” An EORTC study randomly assigned patients age >65 to immediate 3+7 or to observation/supportive care, with use of chemotherapy (hydroxyurea or LDAC) if blood counts worsened or symptoms developed [85]. Median survival was 21 weeks in the 3+7 arm and 10 weeks in the observation arm, and the number of days spent in hospital was essentially identical. However, 80% of the 60 patients enrolled had a performance status <3, and all patients had relatively normal organ function. Furthermore, 50% of the patients randomized to observation had to begin therapy within 1 month, suggesting that they were on the verge of progression when randomized. Thus, data from this trial can be used to support immediate 3+7 only in patients who are relatively fit and likely to progress. In its AML14 trial in patients age >60 not considered fit for 3+7 by community physicians, the NCRI terminated randomization between LDAC and hydroxyurea because of longer survival (medians of 6 vs. 4 months) with

LDAC [86]; number of days in hospital were similar. However similar to the EORTC trial, only 12% of the patients had a performance status of 3–4, with another 18% having a performance status of 2; furthermore, it is unclear, although likely, that hydroxyurea and supportive care are exchangeable. Finally, Tilly et al. found equivalent survival in older patients randomized between LDAC and 3+7, but with less time spent in hospital in the LDAC group; patients with abnormal organ function or poor performance status were excluded [87].

Although the differences in survival between LDAC, 3+7, and supportive care are thus relatively modest, it appears reasonable to administer LDAC to older patients who are unable to receive investigational therapy but have a performance status of Zubrod 0–2, and relatively preserved organ function. Because higher doses of ara-C produce better outcomes in patients with a normal karyotype, use of 3+7 rather than LDAC should be strongly considered in such patients. In contrast, in patients with poor performance status or age ≥ 80 , supportive care should be the first option given the TRD rates listed in Table 1.1 and the absence of data suggesting benefit from LDAC or 3+7. Similarly, a low and stable WBC would add support to a choice of supportive care, since experience suggests that at least some such older patients can survive for 1–2 years without undue morbidity.

1.2.15 Investigational Therapies

1.2.15.1 Not Involving SCT

Table 1.5 [88–100] lists various investigational agents in clinical trial. I will divide these into “noncytotoxic” (NCT) and “cytotoxic” (CT). Examples of the former are tipifarnib, flt3 inhibitors such as PKC412 and CEP701, hypomethylating agents such as decitabine, and agents such as oblimersen that act to accelerate the apoptosis of AML blasts. Examples of CT agents are clofarabine and cloretazine. Although NCT, but not CT, agents are often viewed as “targeted,” it should be kept in mind that CRs following use of standard CT agents result from the greater sensitivity of AML blasts than normal cells, i.e., targeting. Clinically the principal differences between NCT and CT agents are the lower presumably TRD rates with NCT, consequent to lack of effect on organs such as the lung or gut. Table 1.5 illustrates that CR rates seem highest when NCT drugs

Table 1.5. Examples of new drugs being tested in AML

Drug class	Example	Patients	CR rate	Response < CR rate	Effect on survival	Ref.
Farnesyl-trans-ferase inhibitor	Tipifarnib	170 untreated, median age 73	18%	16%	Median 5.6 months	[88]
FLT3 inhibitor	PKC412	20 relapsed/refractory	5%	35–70%	Not stated	[89]
	CEP701	14 relapsed	0%	36%	Not stated	[90]
		24 untreated age > 65 & not considered fit for more standard therapy	0%	32%	Not stated	[91]
Proteasome inhibitor	Bortezomid (+ idarubicin & cytarabine)	12 untreated (age > 60) and relapsed	33%	42%	Not stated	[92]
Hypo-methylating agent	Decitabine	36 with MDS	28%	59%	Mortality rate at 8 weeks 7% vs 26% with AML-type therapy	[93]
	Decitabine + all-trans retinoic acid (ATRA)	29 age > 60 and not eligible for standard induction for untreated AML	14%	17%	Median 7.5 months	[94]
Nucleoside analog	Clofarabine	28 untreated age > 70, or > 60 & not considered fit for more standard therapy	59%	11%	19% induction mortality rate	[95]
Alkylating agent	Cloretazine	28 relapsed/refractory	4%	Not given	Median survival 9 weeks	[96]
Enhancer of apoptosis	Bcl-2 antisense (oblimeresen sodium) (+ daunorubicin & cytarabine)	29 untreated age > 60	48%	10%	Not stated	[97]
P glycoprotein inhibitor	Zosuquidar (+ daunorubicin & cytarabine)	16 untreated and relapsed	69%	6%	Median 18 months	[98]

are combined with standard CT agents, or when the new agent (e.g., clofarabine) bears some resemblance to traditional CT. Nonetheless, patients at high risk of TRD might still initially receive NCT given the risk of TRD with CT (Table 1.3). In contrast, patients at lower risk of TRD might begin therapy with a combination of an NCT agent and standard CT or with an investigational

CT agent (Table 1.3). This is particularly the case since much of the morbidity and mortality associated with AML results from bone marrow failure, which is most rapidly reversed by producing a CR; indeed, as discussed below, it appears that responses < CR are less effective at prolonging survival than is CR.

Table 1.5 (continued)

Drug class	Example	Patients	CR rate	Response <CR rate	Effect on survival	Ref.
Anti CD33 antibody attached to toxin	Gemtuzumab ozogamycin [GO] (+daunorubicin & cytarabine or + fludarabine & cytarabine & idarubicin)	64 untreated age <60	84%	–	80% alive with median follow-up (f/u) of 8 months	[99]
	GO (+daunorubicin + cytarabine)	53 untreated age <60	83%	–	68% alive with median f/u 9 months	[100]
	GO (+cytarabine) Gemtuzumab ozogamycin	21 age >60	43%	–	48% alive with median f/u 7 months	

Not all investigational therapies need involve new drugs. For example, for many years it was thought that no more than 60 mg/m² of daunorubicin could be given daily×3 when combined with standard dose ara-C. However, perhaps reflecting improvements in supportive care, data from CALGB indicate that the MTD is ≥90 mg/m² daily×3 when given with standard dose ara-C + etoposide. This result has prompted an ECOG trial randomizing patients among the 60 and 90 mg/m² daily×3 schedules [101]. By analogy to ara-C this approach might be most useful in young patients with normal karyotype or CBF AML.

There is little doubt of the existence of myeloid leukemia-specific antigens. These antigens underlie the graft-versus-leukemia (GVL) effect. The most obvious proof of the existence of GVL is the reinduction of remission by donor lymphocyte infusions after failure of SCT [102]. An example of a leukemia-associated antigen is PR1, an epitope of proteinase 3 (PRTN3), a serine protease expressed in the azurophilic granules of myeloid leukemia cells (CML and AML) at two- to five-fold the amount found in normal myeloid cells. Molldrem et al. suggested that failure of myeloid leukemia patients to spontaneously develop an immune response PR1 resulted from overexpression of PRTN3 leading to apoptosis of PR1-specific high-avidity cytotoxic T-lymphocytes (CTL) [103]. Vaccination with PR1 has been studied under the hypothesis that it might increase PR1 immunity if done when the number of AML blasts had

been reduced, e.g., following chemotherapy. Clinical responses have followed PR1 vaccination of patients with AML [104] and have occurred only in patients in whom there was at least a two-fold increase in the number of PR1-specific CTL; in contrast there was no relation between response and the number of CTL directed against the “control” antigen PP65. Immune response was indeed more common in patients who had minimal residual, rather than overt, disease when beginning vaccination. A trial in which patients in CR will be randomized to receive or not receive PR1 vaccine was initiated in late 2006. Wilms tumor antigen-1 (WT-1) is also an AML-specific antigen; a vaccine against WT-1 has produced responses in early phase trials [105, 106].

1.2.15.2 RIC SCT

As noted above, TRD is a major reason that survival after allo SCT is not superior to that seen with CT. The use of reduced intensity conditioning (RIC) is intended to address this problem. Although it was believed that much of the efficacy of allo SCT stemmed from the high doses of chemotherapy/radiation made possible by the transplant, current thinking assigns more of a role to GVL. If GVL, not high dose chemotherapy, is the principal mediator of the effectiveness of allo SCT, it becomes feasible to employ RIC SCT (“minitransplant”), thus reducing TRD. Tibes et al. described a systematic attempt to perform minitransplants

in first CR in all MDA patients age ≥ 50 with an abnormal karyotype and a sibling or matched, unrelated donor [107]. Matching for known prognostic factors suggested that the 14 who were transplanted had better outcomes than the 83 who were not, but these 14 represented only 5% of all treated patients age > 50 with abnormal karyotypes. These results question the general applicability of minitransplant and suggest that it might be done before patients enter first CR so as to increase the number of patients who might be candidates given the low CR rates in older patients (and high-risk younger patients). For example, older patients might initially receive an NCT agent. While waiting to see this agent's effect, a donor search might be completed, as might various logistical arrangements. Minitransplant would be performed once the response to the NCT agent is known.

1.2.15.3 SCT

An important development has been the introduction of new radioimmuno-conjugates as part of the pretransplant preparative regimen [108]. For example, Pagel et al. have shown that addition of ^{131}I -anti CD45 antibody to a busulfan/cyclophosphamide (Bu/Cy) conditioning regimen may improve outcome of allo SCT in first CR relative to that seen with Bu/Cy [107].

1.2.16 New Response Criteria

For many years response to induction therapy for AML was classified as CR or no CR. As seen in Table 1.5, responses less than CR have recently been recognized [109]. An example is CRp, i.e., CR with incomplete platelet recovery. Attaining CRp suggests that a treatment is more "active" than if, despite survival time sufficiently long to observe CR or CRp, neither response occurred ("resistant"). However, it is also important to assess whether CRp conveys clinical benefit, i.e., lengthens survival relative to resistant. This appears to be the case [110]; however, little information is available regarding responses such as "hematologic improvement" or "marrow CR."

1.2.17 Therapy for Relapsed or Refractory AML

Most patients with AML will require "salvage therapy" because of failure to enter CR after initial treatment ("primary refractory") or, more typically, relapse after a brief CR. As with therapy for untreated disease, the type of salvage therapy administered should depend on expected outcome with standard salvage regimens such as high-dose ara-C or fludarabine + ara-C. The factors most predictive of response are the duration of the previous remission (zero in primary refractory patients) and the number of previous salvage attempts [111, 112]. If the first CR lasted less than 6 months to 1 year, standard regimens produce CR rates averaging 10–20% when used as first salvage and $< 5\%$ in > 1 first salvage. In contrast, first salvage CR rates in patients with first CRs > 1 -year average 40–50%. Accordingly, the first treatment option in patients with short first CRs or who are receiving > 1 first salvage is investigational therapy. If such therapy is not available, an argument can be made for a supportive care only approach. A stronger case for standard regimens can be made in patients with longer first CRs. Allo SCT can also be used for salvage or in second CR. Its potential value is suggested by Wong et al.'s observation [113] that survival in 135 patients who were either primary refractory or beyond first salvage was similar to that reported by Breems et al. [114] in 507 first salvage, nonprimary refractory patients, who presumably had a better prognosis than Wong et al.'s patients, but only 20% of whom received an allo SCT. Outcome of allo SCT is clearly better in second CR than in first relapse, often prompting a desire to postpone the procedure until second CR. Nonetheless, allo SCT in first relapse may still be superior to chemotherapy in first relapse (the real comparison of interest), even in the presence of circulating blasts, which is associated with a much greater reduction in the effectiveness of allo SCT than in the effectiveness of chemotherapy [113]. Of course, as with allo SCT in first CR, various selection biases likely affect these conclusions.

1.2.18 Treatment of Minimal Residual Disease (MRD)

Most patients ostensibly in remission have residual AML that eventually becomes apparent, leading to diagnosis of "relapse." Detection of MRD would in principle

permit treatment to be changed before relapse and to be discontinued in patients with levels of MRD sufficiently low that relapse is very unlikely. Since relapse can only be diagnosed when >5% blasts are present in the marrow, the sensitivity of morphologic examination of the marrow for detection of relapse is only 1 in 20. In contrast, if 30 metaphases are examined, cytogenetic examination has a sensitivity of 1 in 30, while fluorescent *in situ* hybridization typically has a sensitivity of 1 in 500. Polymerase chain reaction (PCR) techniques allow detection of transcripts of such fusion genes as *RUNX1-CBFA2T1*, *CBFB-MYH11*, or *PML-RAR α* (characteristic of acute promyelocytic leukemia) at a frequency of $\leq 10^{-4}$. Assays for NPM1 have been proposed as another means of MRD detection [114].

Although the molecular abnormalities described above are not detectable even at diagnosis in many patients, all patients may have blasts characterized by aberrant surface marker expression; for example, the same blast may display markers characteristic of both an early and a later stage of differentiation. These patterns are quite specific for AML, as opposed to normal blasts. Once detected at diagnosis, such leukemia-associated immunophenotypes (LAIPs) can thus be used to serially assess MRD. Flow cytometric methods allow detection of 1 cell expressing an LAIP among 1 000–10 000 normal marrow cells [115].

The detection of MRD does not necessarily mean relapse is inevitable. Hence, although more sensitive methods of MRD detection will lead to more sensitivity for diagnosis of subsequent relapse, specificity must also be assured before using a method of MRD detection to guide clinical decisions. Currently, flow cytometry to detect LAIP appears to be both reasonably sensitive and specific [116, 117]. Thus, Kern et al. reported that the change in the number of LAIP+ cells between diagnosis and the end of either induction or consolidation therapy predicted subsequent RFS independent of cytogenetics and in both patients with intermediate or unfavorable cytogenetics [116].

1.2.19 Clinical Issues

Several practices which may have little effect on mortality, but considerable effect on patients' lives, should be mentioned:

1. Hospitalization. Given the more serious nature of hospital-acquired than community-acquired infec-

tion, routine hospitalization during induction or postremission therapy should be discouraged. In addition to the possibility of infection being passed from one hospitalized patient to another by medical personnel who fail to wash their hands, it has been pointed out that hospital water distribution systems may serve as reservoirs of aspergillus and other molds that are aerosolized and subsequently inhaled. The possibility of hospitalization in the typical "reverse isolation" room has little effect on this recommendation.

2. Masks and avoidance of crowds. The advice to avoid crowds flies in the face of observations that bacteria and fungi, rather than viruses, are the typical causes of infection. The bacteria are invariably residents of the patients' own skin (e.g., staph), mouth (*Pseudomonas maltophilia*), or intestines (gram-negative bacilli). The fungi are similarly found on the skin (*Candida*) or are airborne (*Aspergillus*). However, it is unlikely that masks will restrict entry of *Aspergillus* into the nose.
3. Fresh fruits and vegetables. Because there is no evidence that avoidance of these foods lessens the risk of infection, we are conducting a randomized trial in which patients are either encouraged to eat fresh fruits and vegetables or advised not to eat them. Similarly, there are no data suggesting that exposure to flowers or plants is detrimental.
4. Antidepressants. It is the author's opinion that symptoms such as persistent nausea or lack of appetite after completion of chemotherapy are often symptoms of depression. Another perhaps underappreciated cause is antibiotics. Megestrol acetate ("megace") may also be useful to promote appetite.

1.2.20 New Approaches to Clinical Trials in AML [118]

Randomized trials in patients with AML typically enroll 100–200 patients per treatment arm. Such numbers are needed to have 80% power (type 2 error 20%) to detect frequently small absolute differences with a false positive rate (type 1 error) <5%. These rates are sensible when studying a new drug in a disease where standard treatment is reasonably good, and thus where the principal concern is to prevent use of a falsely promising drug that might usurp standard therapy. In contrast, AML is a disease for which there is often no satisfactory

treatment. Thus, there may be more reason to protect against a false negative than a false positive result. At the least, it might be reasonable to specify type 1 and type 2 errors of 20% each. Such a change together with an interest in detecting only larger, more clinically meaningful, differences would enable fewer patients to be entered per treatment arm, thus allowing more treatments to be studied [119]. While such trials would be nominally “underpowered,” this ignores the false negative rate inherent in the selection of which, of many, investigational regimens to study. For example, if there are three potential regimens that could be investigated and if preclinical rationale is an imperfect predictor of clinical results, limiting investigation to one regimen potentially entails a false negative rate of 67%. In particular, the most egregious false negative results when a treatment is not studied at all [119]. This is problematic since, although by no means exhaustive, Table 1.5 lists nine different classes of drugs undergoing investigation. Use of each class rests on a presumably sound preclinical rationale, and each class may contain many drugs. Furthermore, there may eventually be combinations of drugs across classes.

Patients with poor performance status or other factors likely to increase TRD are often ineligible for clinical trials, although the development of new NCT agents might particularly benefit such patients. Even when eligible, patients may be excluded because it is believed they will do poorly. Although the extent of this subtler form of selection bias is unknown, papers reporting results of clinical trials only infrequently note that consecutive patients were entered and treated. Obviously the greater the extent of such bias the less likely it becomes that results will be reproducible in a more representative group of patients.

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Hematologic Malignancies: Acute Leukemias
Faderl, S.H.; Kantarjian, H.M.; Estey, E.H. (Eds.)
2008, X, 294 p., Hardcover
ISBN: 978-3-540-72302-8