

“3+7” Therapy for the Treatment of Acute Myeloid Leukemia

PRO

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I have used the combination of an anthracycline and cytarabine, known as “3+7,” as induction therapy for acute myeloid leukemia (AML) for more than 30 years and would love to replace it with a worthy successor that would improve the overall stagnant results of the treatment of AML. However, the 3+7 regimen, which typically consists of 3 days of daunorubicin, 45–60 mg/m² each day, and 7 days of cytarabine by continuous infusion at a daily dose of 100 mg/m², has a consistent track record and has been of substantial benefit to many thousands of patients. Complete remission (CR) rates of 65–75% or higher are achieved in younger patients, with many being cured of their disease, while approximately 50% of adults 60 years of age and older attain CR. With improvements in supportive care, most treatment failures are a consequence of the persistence or rapid regrowth of leukemia due to drug resistance.

Considerable laboratory and clinical efforts have focused on determining the “Achilles heel” among multiple mechanisms of drug resistance, but approaches by which drug resistance can be overcome remain elusive. There have been a host of randomized trials attempting to improve upon these CR rates, but remarkably—and unfortunately—none have been consistently successful. These strategies have included:

- the addition of thioguanine (GlaxoSmithKline) or etoposide to 3+7;
- prolonging the infusion of cytarabine to 10 days or doubling the dose of the cytarabine;
- the use of high-dose cytarabine in combination with the anthracycline;

- the addition of modulators of P-glycoprotein in an attempt to overcome the multidrug resistance phenotype;
- anthracycline “roulette” with substitution of idarubicin, doxorubicin, mitoxantrone, rubidazole, or aclacinomycin for daunorubicin;
- the use of hematopoietic growth factors given either during or after the 3+7 chemotherapy;
- modulators of the cellular metabolism of cytarabine; and
- various attempts at intensifying induction with “timed sequential” or “double induction” strategies.

Nor is there compelling evidence that any of these approaches have produced better “quality” remissions as might be suggested by improvements in event-free or overall survival, although differences in postremission treatments can obviously affect event-free survival and overall survival rates. The striking similarity among these results, which remain unchanged if one includes patients with short durations of CR as “nonresponders,” suggests that there is a significant fraction of AML patients whose leukemic stem cells are resistant to available chemotherapeutic manipulations and who may need very different approaches to treatment. Some of these patients can be identified prospectively by cytogenetic analyses, marrow morphology, or clinical histories indicative of prior myelodysplasia. Many of these primarily resistant leukemias are probably derived from a cell that is close to the hematopoietic stem cell. Hematopoietic precursors are designed to survive the repeated exposures to environmental toxins expected to be encountered during a lifetime. Virtually all resistance mechanisms studied to date have been overexpressed in such cells. As demonstrated by marrow purging experiments, the hematopoietic stem cell can survive exposure to very high doses of cytotoxic agents *in vitro*. It is not surprising, therefore, that leukemias derived from such immature progenitors are particularly resistant to cytotoxic agents. The complexity of the mutations in AML in older patients or in those with prior myelodysplasia may actually be more analogous to the multiple changes found in epithelial cancers than to the balanced translocations common in AML in younger patients. Interestingly, there is virtually no understanding

of drug sensitivity or why these other subtypes of AML can be cured using identical chemotherapy.

The large number of randomized trials and pilot studies of induction chemotherapy are indicative of the frustrations of leukemia investigators with their inability to improve upon the overall results of AML treatment over the past 10–15 years. Indeed, it can be argued that improvements in antiemetics, which permit induction and consolidation therapy to be given more safely, may have been the major advance during this period, particularly in older patients. So where should we go from here? Some current national group trials are evaluating either dose escalation of the anthracycline or the addition of gemtuzumab ozogamicin (Mylotarg, Wyeth) to 3+7. These approaches are certainly worthy of study, although the results enumerated above do not encourage optimism about the effects of such chemotherapy “type” manipulations.

In the absence of a drug affecting a specific target that can be identified at diagnosis, there is debate about how to study new approaches to induction. Possibilities include:

- **Adding new agents to 3+7.** This can be difficult to do if there are overlapping toxicities of the new drug with the anthracycline or cytarabine such that the dose of either may have to be decreased. It may, however, be possible to add noncytotoxic agents (flt-3 inhibitors, antiangiogenesis agents, proapoptotic compounds [such as bcl-2 inhibitors]) to full-dose 3+7, and then compare the 2 regimens in a randomized trial.
- **Substituting a new agent for either the anthracycline or cytarabine.** There is little information about which is the more critical of the 2 components of 3+7 therapy, and there is a risk of compromising the outcome unless the new drug is truly a winner. Since 3+7 is well tolerated, producing equivalent results with a new agent would be of less interest.
- **Forgetting about 3+7 and using entirely new regimens.** This approach is mentioned most often in older patients or those with secondary leukemia or prior myelodysplasia because of the very poor long-term outcome in such individuals (ie, “it’s hard to do worse”). However, conventional induction therapy is not totally futile since approximately 20–30% of such patients reach CR with relief from the risks of the cytopenias that accompany untreated AML. Although the benefit for responders is usually measured in months rather than years, ineffective therapy is of no benefit and usually equates with death from infection or other complications. Unlike other cancers, there is generally only one initial opportunity to achieve response because of the increasing mortal-

ity associated with prolonged periods of cytopenia; initial ineffective treatment could deprive a patient of the limited, but real, benefits of more standard induction regimens.

Thus, any totally new regimen should generally have compelling results in relapsed patients prior to its use upfront. A recent exception might be the experience with the orally administered farnesyl transferase inhibitor tipifarnib (Zarnestra, Johnson and Johnson), which has shown some intriguing results as initial induction in “frail” older patients who were felt not to be candidates for chemotherapy, but which produced dismal response rates in patients with relapsed or refractory AML. It remains to be seen whether the preliminary results will be substantiated in larger multi-institutional trials and whether this is an accurate precedent for other drugs that may not turn out to be active.

Evaluating New Agents as Postremission Therapy

There are a number of possible study designs for the evaluation of new agents in patients with AML in first remission, perhaps the most attractive of which is evaluating the new agent during both induction and consolidation. Another approach, particularly for noncytotoxic agents, is randomization between observation versus the new drug after completion of standard postremission treatment.

Trial Designs to Rapidly Screen New Regimens

Another approach to rapidly screen new ideas is a series of randomized phase II trials that are not designed to definitively prove superiority, but rather to identify regimens that might be the “best bet” to move onto more definitive phase III studies. Although there is a risk of false negatives (ie, missing active treatments because of small numbers of heterogeneous patients), this approach offers the possibility of more rapid screening of different strategies.

Practical Problems

AML is not a common disease, and most patients in the United States are not seen in university or research centers, and a small fraction are registered on clinical trials. Indeed, it is conceivable that some of the “negative” trials mentioned above could have been “positive” if, as in recent trials in solid tumors, thousands of patients could have been randomized with a power to detect differences of a few percentage points.

In order to address the promises of new approaches efficiently, it is necessary to develop administrative sys-

tems that more effectively channel patients to trials asking innovative questions with supportive *in vitro* correlates. The current mechanisms are tedious and at times frustrating. A national leukemia trials consortium encompassing the current efforts of the cooperative groups is one important consideration; such disease-focused groups in the hematologic malignancies have been quite successful in Europe.

Another issue is that most new agents are under the control of pharmaceutical companies, which tend to have highly focused agendas that can be intolerant of tinkering with doses, schedules, and combinations. In addition, if the combination of 2 or more investigational agents from different companies is deemed worthy of study, the administrative barriers to be overcome can be considerable, to say the least.

But, improvements are needed and soon. The real issue is not whether 3+7 remains the standard regimen but rather how to advance treatment so that in the next decade, I will have to learn how to enthusiastically order new and more effective regimens for AML and its virulent cousin, myelodysplasia.

CON

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The standard therapy for untreated AML, commonly known as “3+7,” is administered to the majority of patients. However, the use of 3+7 is not the optimal treatment for the great majority of patients. Variants of 3+7, such as those substituting daunorubicin with either idarubicin or mitoxantrone, or those adding granulocyte-colony stimulating factor (G-CSF) or granulocyte-macrophage colony stimulating factor (GM-CSF), should be considered as an equivalent of 3+7 therapy, based on numerous randomized trials.

Older Patients

Older patients would benefit most from treatment with therapy other than 3+7 or its variants. Survival after treatment for AML worsens with each increasing year of age. For practical purposes, patients aged 60 and older are typically regarded as elderly. Approximately 25% of such patients given 3+7 therapy die before response, whether a CR or not, (ie, within 6–8 weeks of starting therapy). A

25% 2-month mortality rate is, most likely, worse than what would be expected without treatment.

These data must be interpreted in light of the outcomes of the 75% of patients whose death is not hastened by 3+7 therapy. Clearly, there is more rationale for the use of this regimen if it leads to long-term survival in many patients. However, at most two thirds of the 75% experience a CR, for an overall CR rate of, at most, 50%.

Achieving CR is important largely because it is required for long-term survival. However, by itself, CR is inadequate for the purpose of achieving long-term survival. Indeed, median relapse-free survival (RFS) in older patients who receive 3+7 induction therapy followed by the postremission equivalent of 3+7 (4 courses of cytarabine 100 mg/m² daily times 5 days), is approximately 10–12 months, with only 20% of patients who achieve CR alive in CR at 2–3 years. Beyond this time, the likelihood of relapse is so low (<10%) that patients are considered “potentially cured.”

With a CR rate of less than 50% and a 2–3-year survival rate of 20%, the percentage of patients who are potentially cured from 3+7 therapy is approximately 10%. Furthermore, these outcomes are those reported from clinical trials conducted by cooperative groups. Patients with poor performance status or abnormal organ function are routinely ineligible for such trials, yet may constitute 20% of older patients with AML. If these patients were included in clinical trials employing 3+7, the CR rate would be less than 50%.

Taking into account these considerations, it is my opinion that the benefit achieved with 3+7 therapy is insufficient to justify the 25% early death rate. In addition, one must consider the complications induced by 3+7, which include a 15–20% incidence of each of severe dyspnea, infection, and malaise.

Fifteen years ago, in what has proven to be an influential randomized trial, Lowenberg et al compared the outcomes of 60 patients age 65 years and over, 31 of whom were given a 3+7 variant at diagnosis and 29 of whom were given transfusions, with chemotherapy added only for leukemia-associated complications. All patients had a good pretreatment performance status. Median survival was 21 weeks in the patients treated at diagnosis and 11 weeks in the patients in whom therapy was delayed. The group given 3+7 therapy spent a median of 55% of their remaining life in the hospital, and the corresponding figure in the latter group was 50%, with time in hospital being a useful indicator of morbidity.

Although the study by Lowenberg et al is often cited as evidence that 3+7 is better than no treatment, I question its general relevance. First, the median time from randomization to the supportive care arm to initiation of therapy was only 9 days. In contrast, my experience

suggests that, not infrequently, patients with active AML can live months without treatment and can spend more of their life after diagnosis out of remission than in remission. Second, the treatment given to the supportive care group upon progression was single-agent cytarabine or hydroxyurea, each very plausibly being less effective against AML than 3+7 therapy. It may be that a comparison of the 3+7 regimen versus supportive care followed by 3+7 upon progression would show a benefit for the latter approach, which, in particular, might produce less early mortality.

The argument in the preceding paragraphs ignores the variability in outcome observed even in older patients after use of 3+7. Thus, it is appropriate to ask whether there are patients age 60 or above for whom 3+7 might be an acceptable choice. Since cytogenetics is a major determinant of outcome in AML, an obvious group might be patients with inv(16) or t(8;21), abnormalities known to be sensitive to cytarabine. However, these patients are known to benefit from higher doses of cytarabine, raising the possibility that they should receive such doses, as discussed in more detail in the section on younger patients.

Turning to older patients without inv(16) or t(8;21), examining a combination of prognostic covariates is often helpful. With this in mind, I will use pretreatment characteristics to define 2 groups of older patients. Group 1 comprises those patients who have at least 1 of the following: an abnormal karyotype, a history of abnormal blood counts preceding the diagnosis of AML by at least 1 month, secondary AML, a serum bilirubin or creatinine greater than 1.9 mg/dL, or a performance status of 3 or 4. Group 2 is comprised of those patients with none of these characteristics. At the University of Texas M. D. Anderson Cancer Center (MDACC), we have made little use of 3+7, but do have data on 65 patients treated with 3+7 variants in the early 1980s. Table 1 shows their outcomes according to group.

Although the patients were treated many years ago, the overall CR rate and median survival are reasonably representative. Twenty percent of the patients are in the more favorable group (Group 1). Informed patients in this group might be very willing to accept 3+7. However, informed patients in group 2 would, most likely, not be willing to undergo 3+7 therapy. Thus, while it is reasonable to offer 3+7 therapy to older patients with a more favorable prognosis, the same is not true for the 80% of older patients who fall into the less favorable prognostic group.

I believe patients in the less favorable prognostic group should be entered into clinical trials for new therapies. Although the “bench-to-bedside” paradigm has obvious appeal, most successful treatments for leukemia (interferon for chronic myelogenous leukemia; cladribine [Leustatin, Ortho Biotech] for hairy cell leukemia, all-trans retinoic acid and arsenic trioxide [Trisenox, Cell

Table 1. Outcomes of AML Patients Age ≥ 60 Years Treated With 3+7 Variants

	All Patients	Group 1	Group 2
Patients, n	65	13	52
CR, n (%)	33 (51%)	10 (77%)	23 (44%)
Median survival, wk	32	48–51	20
Probability of being alive in first CR at 1 year from start of treatment, %	22	39	15
Probability of being alive in first CR at 2 years from start of treatment, %	13	23	11

AML = acute myeloid leukemia; CR = complete response.

Therapeutics] for acute promyelocytic leukemia) have had an empirical derivation. In contrast, many treatments with apparently compelling rationales, such as the use of G-CSF or GM-CSF as supportive care or for “priming” of AML blasts, have been less successful. Our knowledge about the difference between AML cells and their normal counterparts is quite limited, and thus it is essential to conduct as many different clinical trials as possible, because we do not know a priori which approaches will improve outcome.

Given our limited knowledge, it is not surprising that most strategies evaluated in clinical trials do not show a survival benefit. However, precisely because our knowledge is thus constrained, it is always plausible that a given clinical trial will turn out to lead to a therapeutic advance. By contrast, sufficient experience shows that 3+7 is unlikely to benefit patients, particularly those in the poor prognostic group described above. Allocation of the majority of AML patients to 3+7 therapy slows the pace of research and thus the identification of potentially effective therapies.

Relatively poor-prognosis (group 2) older patients who are unable to participate in a clinical trial should be considered for palliative care. When informed about the outcomes of 3+7 therapy in poor-prognosis patients, many patients would most likely prefer palliative care. More likely, they would view both 3+7 and palliative care as unsatisfactory. Such patients might then inquire about the difficulty of enrolling on a clinical trial, perhaps prompting eventual wider availability of trials.

Younger Patients

The principal reason to avoid 3+7 in older patients is that the potential benefits do not justify the approximate 25% risk of early death. In younger patients, this risk is much less (5–10%). Rather, the reason not to treat younger patients with 3+7 is that more effective regimens are likely available. These regimens emphasize dose intensity, particularly of cytarabine.

The Cancer and Leukemia Group B (CALGB) conducted an important study evaluating cytarabine dose intensity for AML. In this study, patients in CR were randomized after 3+7 therapy to 4 courses of cytarabine at either 100 mg/m² daily × 5 days by continuous infusion, 400 mg/m² daily × 5 days by continuous infusion, or 3 g/m² every 12 hours on days 1, 3, and 5. Subsequently, patients received 4 monthly treatments of cytarabine 100 mg/m² twice daily × 5 days, with daunorubicin on day 1.

This study found that among older patients, the CR rate was 47%, with a 7% probability of being alive in CR 5 years after beginning treatment, regardless of cytarabine dose. In younger patients, outcomes varied by cytogenetic group and cytarabine dose (Table 2).

The effectiveness of the 3 g/m² dose level is unknown; British Medical Research Council (MRC) trials have found similar results in patients with inv(16) or t(8;21) who were treated at the 1 g/m² dose level. However, the findings of the CALGB trial illustrate the strong relationship between dose and outcome in these patients and in those with a normal karyotype.

This relationship has also been observed with induction therapy. The primary reason for treatment failure in younger patients is relapse. Thus, it is noteworthy that changes in induction therapy can affect outcome once patients are in CR. For example, a randomized Australian trial in patients under age 60 compared 3+7 plus etoposide with the same regimen, but with cytarabine at 3 g/m² twice daily on days 1, 3, 5, and 7, rather than 100 mg/m² daily × 7 days. Postremission therapy was uniform, including cytarabine at 100 mg/m². CR rates were the same, but patients given the higher cytarabine dose had a 48% probability of RFS at 5 years, versus a 25% probability in the group receiving 3+7 plus etoposide. Similarly, the Children's Cancer Study Group (CCSG) found that children and adolescents who received a second course of a 3+7 variant regimen on day 10 of course 1 had longer remissions and survival than patients given a standard 3+7 variant regimen with the second course not begun before day 14 and begun only if blasts persisted or reappeared in the marrow. This finding occurred even when the same postremission therapy was employed.

Taking into account that choice of induction regimen can affect length of CR, is there evidence that use

Table 2. Results in Younger AML Patients By Cytogenetic Group and Cytarabine Dose

Cytogenetics	Patients randomized in CR	Probability of RFS at 5 years by cytarabine dose, mg/m ²		
		100	400	3,000
Inv 16 or t(8;21)	57	16%	57%	78%
Normal	140	20%	37%	40%
Other	88	20%	20%	20%

AML = acute myeloid leukemia; CR = complete response; RFS = relapse-free survival.

of doses of cytarabine higher than those given with 3+7 produce longer remissions if therapy is intensified once CR occurs? The CCSG study provides such evidence, given that remissions were longer in patients given intensive, rather than standard, timing during induction even if both groups received the same myeloablative therapy (autologous or allogeneic transplant) once in CR.

A similar observation was made in a French trial in which patients were randomized to receive 3+7 (using 80 mg/m² daunorubicin, rather than the usual 45–60 mg/m²), a double induction arm in which a second course began on day 21 regardless of marrow findings, and a “timed-sequential” arm, analogous to that used by the CCSG, in which patients received an additional 500 mg/m² cytarabine every 12 hours on days 8–10. In CR, 1 course of cytarabine 500 mg/m² on each of days 1–3 and 8–10 was given to each group, while patients with a sibling donor received an allogeneic transplant. RFS was superior in patients under age 50 given timed sequential induction therapy, although survival was unaffected.

The Southwest Oncology Group (SWOG) also conducted a study evaluating an induction/postremission therapy more intense than 3+7. In this study, patients under age 65 years were randomized to receive either 3+7 (SDAC) or the same daunorubicin dose plus cytarabine 2 g/m² every 12 hours for 12 doses (HDAC). Once patients in the SDAC group were in CR, they were randomized to receive either continued SDAC (2 courses) or HDAC (2 or 3 g/m², 1 course). Patients given HDAC received a further HDAC course in CR. Event-free survival and overall survival were each best in patients given HDAC as both induction and post-CR therapy.

The SWOG and French studies are open to criticism because the HDAC given post-CR was not given for as long as the HDAC given post-CR in the CALGB trial noted above. Indeed, in the SWOG trial, there was no evidence that postremission therapy (SDAC or HDAC)

affected length of CR in patients given SDAC during induction (again, unlike the CALGB results). Similarly, it can be argued that type of induction therapy did not influence survival in the French trial. However, such an influence was observed in the CCSG trials.

Thus, the above data place the burden of proof on those who contend that healthy patients under age 50–60 years should not receive a more intense regimen than 3+7 during induction, as well as during consolidation. In particular, while this approach conveys an increased risk of induction death (11% vs 4%, 13% vs 5%, and 16% vs 12% in the CCSG, SWOG, and French trials, respectively), the likelihood of treatment-induced mortality is more than counterbalanced by the likelihood of long-term benefit, including survival in the SWOG and CCSG trials. Furthermore, advances in supportive care that would reduce the risk of higher intensity induction regimens are more likely than advances in post-CR therapy that would improve long-term outcome in patients given 3+7.

However, intensified induction therapy, such as increased dose or timing of cytarabine, for patients with abnormalities of chromosomes 5 and/or 7 is not recommended, as there is sufficient evidence (eg, the CALGB data noted above) that such patients are unlikely to materially benefit from this approach. Rather, because induction therapy is likely to affect post-CR outcome, patients with these abnormalities should receive investigational therapies beginning at presentation.

Summary

Table 3 summarizes my view on induction therapies for untreated AML. Assuming the median age of patients with untreated AML is 65 years, these recommendations would result in at most 10–15% of patients receiving 3+7 therapy. This approach requires that cytogenetic results, which may take 2–3 weeks to determine, be known before induction therapy begins, *(continued on page 141)*

Table 3. Recommended Induction Therapies for Patients With Untreated AML

Age	Risk Factors	Induction Therapy	Comment
60 or above	At least 1 one of: abnormal cytogenetics, antecedent hematologic disorder, secondary AML, Zubrod performance status >2, serum bilirubin or creatinine >1.9 (80% of patients age 60 and above)	Investigational	Risk of death and morbidity with 3+7 not commensurate with likely benefit; palliative care if investigational therapies unavailable
	None of above risk factors	3+7 or investigational	Risk of death and morbidity with 3+7 plausibly commensurate with likely benefit
59 and below	Not -5/-7 cytogenetics (80% of patients 59 and below)	Intensified dose of cytarabine or intensified timing	Likelihood of superior outcome post-CR justifies somewhat increased risk of induction death
	-5/-7 cytogenetics	Investigational	Likelihood of poor outcome even with intensification approaches; 3 + 7 if investigational approaches unavailable

AML = acute myeloid leukemia; CR = complete response.