Treatment of acute myeloid leukemia in the elderly

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In this issue of Haematologica, Itzykson *et al.* for the ALFA group show that the choice of post-remission therapy has seemingly little effect on duration of survival after complete remission in patients aged 65-70 years old with acute myeloid leukemia (AML).[1] In more detail, survival times were similar between patients treated with: (i) six courses of relatively "less intense" outpatient therapy, (ii) one course of inpatient therapy containing 45 mg/m^2 daunorubicin (or 9 mg/m^2 idarubicin) daily on days 1-4 + 200 mg/m^2 cytarabine daily on days 1-7 thus amounting, in total, to four times more anthracycline and 2.5 times more cytarabine than administered in the outpatient regimen, or (iii) two courses of inpatient therapy with a 4- to 6-fold increase in anthracycline and over 10-fold increase in cytarabine compared to the outpatient regimen. In contrast, a previous ALFA study found that patients aged 65 years or older who were randomly assigned to the outpatient regimen rather than to the one course inpatient regimen survived longer after achieving complete remission and also had a longer relapse-free survival.[2] The difference did, however, seem more statistically significant (P=0.03) than clinically relevant (median survivals after complete remission of approximately 24 rather than 18 months). In neither study[1,2] was the intensity of post-remission therapy more relevant

in patients who might be inherently more sensitive to anthracycline or cytarabine because they had "intermediate" rather than "unfavorable" prognosis cytogenetics; prognostically "favorable" cytogenetics are very uncommon in older patients. The ALFA investigators' data are consistent with the general consensus that post-remission therapy employing any permutation of anthracyline or cytarabine is unsatisfactory for the vast majority of patents age 60 years or more with AML in first complete remission.

What other post-remission therapies might be offered? In principle perhaps the most attractive is allogeneic hematopoietic cell transplant (HCT). Reduced intensity conditioning (RIC) regimens that reduce toxicity but permit engraftment and subsequent development of T-cell-mediated graft-*versus*-leukemia effects allow even patients in their early 70s to receive a RIC-HCT.[3] Results using matched unrelated donors rival those seen with matched sibling donors,[4] and mortality rates in the period of highest risk (approximately the first 100 days after the HCT) have fallen to a current level of 10-20%.[5] Although HCT is also associated with a subsequent 30% decrease in life expectancy among patients "cured" of their malignancy,[6] the risk of death with RIC-HCT might still be less than the risk without RIC-HCT if the relapse rate is sufficiently decreased. Analyses comparing patients with and without donors, rather than merely patients who were or were not transplanted, suggest that this is the case.[7] However, analyses of patients with donors *versus* those without donors are problematic in remedying a bias in favor of HCT, particularly with unrelated donors.[8] While reducing potential bias, Mantel-Byar statistical methodology is not a substitute for randomizing patients with donors between immediate RIC-HCT and RIC-HCT only when evidence suggestive of relapse is present. Given the increasingly sensitive and specific means of detecting minimal residual disease considerably earlier than the detection of frank relapse, such randomization appears more appealing, although still unlikely to be done. Another issue related to a bias in favor of HCT is that of the general applicability of RIC-HCT.[9] Finally, it is intuitive that pre-HCT minimal residual disease indicates the inadequacy of prior chemotherapy. Thus the observation that the finding of minimal residual disease prior to HCT in patients in first complete remission, using morphological criteria, is a major independent predictor of post-HCT relapse[10] suggests that standard chemotherapy and standard RIC-HCT are not as different as might be hoped. The same can be inferred from reports that cytogenetics that augur high rates of relapse with chemotherapy do the same with RIC-HCT.[11] Indeed relapse remains the major cause of failure of RIC-HCT.[11]

These limitations of RIC-HCT might be overcome by more effective/less toxic conditioning regimens or immunological augmentation of the post-HCT graft-*versus*-leukemia effect. Examples of the former include use of clofarabine or of radiolabeled antibodies to CD45.[12] Immunological augmentation might be achieved using T cells specific for well-defined AML-associated antigens such as WT1, or for minor histocompatibility antigens expressed on host hematopoietic cells but not cells affected by graft-*versus*-host disease.[13]

In turn, immunological approaches might be used as post-remission therapy outside the RIC-HCT setting. For example, Bruns *et al.* randomized 320 patients (80% in first complete remission, 20% in a subsequent complete remission) to receive either a combination of interleukin-2 and histamine or no further treatment after completion of maintenance therapy and typically 4-5 months after entering complete remission.[14] The interleukin-2 and histamine combination prolonged survival and leukemia-free survival by a median of approximately 4-6 months in patients in first complete remission. Although, as is often the case, the improvement in leukemia-free survival but not survival was statistically significant ($P<0.05$), the data prompted the European Medicines Agency to approve the combination of interleukin-2 and histamine for patients in first complete remission.

Table 1. Therapy according to risks of treatment-related mortality and resistance.

	Risk of treatment-related mortality	
	Lower	Higher
Risk of resistance		
Lower	Current intensity	Add new low intensity (ATRA, aza.)
Higher	New high intensity	New low intensity

Just as the covariates predicting response to HCT are those predicting response to prior chemotherapy, the principal covariate predicting response to new drugs is response to older drugs, principally cytarabine and anthracyclines, as evaluated by duration of prior remissions. It follows that it may be easier to discover active new drugs in patients who are in complete remission after cytarabine and anthracyclines rather than in patients who have relapsed or failed to enter complete remission when treated with these drugs (or have yet to receive them, as with newly-diagnosed older patients). Nonetheless new drugs are conventionally first tested in relapsed, refractory, or untreated older patients. While the amount of activity required in such patients to move a drug forward is debatable, there appears to be some movement towards investigation of new drugs in patients in complete remission with or without minimal residual disease. Examples are ongoing studies of decitabine or bortezomib. Furthermore, in the future there is likely to be increasing use of agents whose mode of action, such as specifically targeting AML "stem cells", suggest they would be most effective in patients with relatively small amounts of disease, for example those in complete remission.[15] It is also probable that, instead of being viewed separately, "HCT" and "non-HCT" approaches will be combined to prolong complete remission. Examples are the prophylactic use of azacitidine,[16] or the FLT3 inhibitor AC220, in patients at high risk of relapse after HCT.

New approaches to induction therapy may also prolong remissions given precedents suggesting that different induction regimens can produce similar complete remission rates but be associated with differences in relapse-free survival despite administration of identical post-remission therapy (for example, HCT[17]). However, the primary purpose of induction therapy remains to produce a response that will lead to prolonged survival. For many years this response was thought to mean complete remission. Indeed Walter *et al.*,[18] after accounting for time needed to observe response, cytogenetics, *de novo versus* secondary AML, and

age, demonstrated that although patients who achieved complete remission with incomplete platelet count recovery had a better survival than patients who lived long enough to achieve complete remission with or without platelet recovery but did not do so, relapse-free survival and survival were superior in patients achieving complete remission rather than complete remission with incomplete platelet count recovery. However, these results were observed in patients who received conventional cytarabine-containing therapy, and the relation between complete remission and survival may not be as iron-clad in patients given drugs such as azacitidine. Nonetheless, I believe the goal of induction therapy should still be to produce a complete remission.

With this in mind it is well-known that complete remission rates (and survival from diagnosis) following administration of standard cytarabine and anthracyclines are very variable even in patients aged 60 years or more. Several systems incorporate multiple covariates to assess probabilities of complete remission and survival in such patients with such therapies.[19] These probabilities can be used to decide whether a patient should receive standard induction therapy or participate in a clinical trial. Because results with a given trial are by definition only incompletely known, the decision to opt for a trial largely reflects dissatisfaction with the outcome of standard therapy. A principal determinant of this outcome is cytogenetic (and, increasingly, molecular genetic) status. Because knowledge of this status may be unavailable for several days, physicians may ask whether it is appropriate to await results even in patients with relatively low and stable white blood counts (< 50×10^9/L). However, in my opinion, it is important to avoid giving standard therapy to the many older patients in whom not only may the complete remission rate be less than 20-40% with such therapy but who may incur treatment-related mortality before a second therapy can be given. Furthermore, examining the effect on outcome of time from diagnosis to therapy in 1,361 patients with newly-diagnosed AML and a white cell count less than 50×10^9/L, Sekeres *et al.* found that, after accounting for other covariates associated with outcome, time from diagnosis to therapy had no influence on complete remission or survival in patients aged 60 years old or more.[20]

At least in the USA, single agent azacitidine or decitabine is being used enough to warrant consideration as "standard therapy". Although shown, in a randomized trial[21] involving patients with 21-30% marrow blasts who were typically aged 60 years or above, to be associated with statistically superior survival than (primarily) supportive therapy only, I doubt many older patients would consider the median 8-month survival benefit in the azacitidine arm sufficient to obviate the need for a clinical trial. If a clinical trial is decided on, as I believe use of the various prognostic systems will dictate in the great majority of patients aged 60 or above, the sheer number of trials for such patients suggests that it is not at all obvious what that trial should be. Major issues are the preponderance of trials that refer neither to a historical nor much less to a concurrent control, thus leading to falsely positive results in the subsequent randomized trial that is often excessively large/lengthy reflecting the desire to detect "statistically significant", but perhaps medically, insignificant differences. The size and duration of such trials limit the number of new therapies that can be studied, leading to the increasing use of smaller trials ("play-the-winner") that are randomized from the outset and intended to select one among several therapies to be investigated in subsequent larger randomized trials. Although play-the-winner's randomization among several arms results in decreased power, the hypothesis underlying the design is that the worst false negative is complete failure to investigate a new therapy.

Finally, most trials for newly-diagnosed AML are limited to either patients age under 60 years old or aged 60 or above. The underlying assumption is that age is the most important prognostic factor in AML. However, Walter *et al.*[22] have shown that this is not true with regard to either treatment-related mortality or resistance to therapy. Indeed age can be eliminated from models predicting these outcomes, based on factors such as cytogenetics, with trivial loss of accuracy. Consequently, patients whose resistance score (or treatment-related mortality score) is below the median but are aged 60 or above are less likely to be resistant or incur treatment-related mortality than younger patients with higher scores. Since treatment-related mortality and resistance are the causes of failure in the vast majority of patients with AML, a treatment assignment scheme such as that shown in Table 1 might be more rational than a scheme solely based on age.

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