Should persons with acute myeloid leukemia have a transplant in first remission?

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Despite more than 40 years of extensive study, it remains uncertain which individuals, if any, with acute myelogenous leukemia (AML) in first remission should receive a blood cell or bone marrow transplant versus post-remission chemotherapy (or both). Nevertheless, there is a recent trend toward recommending more transplants in this setting. We consider four myths underlying this recommendation: (1) only individuals achieving second remission benefit from a transplant; (2) there is no effective therapy for relapse other than an allotransplant; (3) we can accurately predict which individuals with AML in first remission need a transplant; and (4) detection of minimal residual disease in first remission will resolve this controversy. We discuss these misconceptions and suggest approaches to resolve this issue.
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All who drink of this remedy recover in a short time, except those whom it does not help, who all die. Therefore, it is obvious that it fails only in incurable cases.-Galen

For more than 40 years, hematologists have debated the best way to prevent relapse and prolong survival of individuals with acute myelogenous leukemia (AML) in first remission: an allotransplant or post-remission chemotherapy. Many analyses were done including comparisons of outcomes from historical databases, controlled trials, pseudo-randomized trials (often based on donor availability), case–control studies, matched-pair analyses, comparison

of outcomes using data from observational databases, meta-analyses of randomized trials and/or observational data-bases, propensity score analyses and more (for example, see Koreth et al.[1]). Statistical techniques used include landmark analyses, Mantel–Byar test, Simon–Makuch plots, conventional and extended Cox regression models, multi-state models and others. Structured qualification of expert opinion was also used. Although a detailed review of this large body of data is not the focus of our report, we discusse advantages and limitations of some of these approaches previously including recent concerns over biases from using fixed-effects models for meta-analyses[2,3].

Most of these analyses show fewer relapses with allotransplants. However, there is disagreement whether leukemia-free survival or survival are improved with transplants. There is also the issue of whether the outcome of reserving transplants for individuals who relapse might not result in a similar outcome to transplanting everyone eligible in first remission, some of whom already cured by prior therapy may die because of transplant-related complications. For example, some analyses indicate a benefit for transplants only in persons with adverse risk factors such as a FLT3 (fms-related tyrosine kinase[3]) internal tandem duplication, whereas other studies report contradictory data or a benefit only in persons with standard or intermediate cytogenetic risk factors[4,5]. Moreover, these analyses focus on population-based outcomes, ignoring the more complex and relevant question of who, if any individual, should receive a transplant in first remission, the level on which physicians need to make therapy recommendations.

For several reasons the recent balance has swung toward recommending more transplants for individuals with AML in first remission. One is the notion that very few persons who relapse achieve second remission which is (mistakenly) considered by some as the only situation where a transplant can help[6]. Other reasons include lack of substantial progress in other post-remission therapies, enthusiasm (appropriate or not) for reduced-intensity transplants and increasing availability of alternative donors such as HLA-matched unrelated individuals, HLA haplotype-mismatched relatives and HLA-matched umbilical cord blood cells. In addition, there is a steady decrease in transplant-related mortality, mostly from better post-transplant immune suppression and supportive care[7].

Although no one really knows what post-remission therapy is best, especially for a specific individual with AML in first remission, we think it is important to consider several common misconceptions: (1) only individuals achieving second remission benefit from a transplant; (2) there is no effective therapy for relapse other than an allotransplant; (3) we can accurately predict which individuals with AML in first remission will relapse and need a transplant; and (4) detection of minimal residual disease in first remission will resolve this controversy. We discuss these misconceptions and suggest a different way to approach the unresolved issue of who with AML should get a transplant in first remission.

The only individuals who relapse and benefit from a transplant are those achieving second remission

Results of transplants in individuals achieving second remission are clearly better than results of transplants in individuals who receive reinduction chemotherapy, fail to achieve second remission and are then transplanted. Bien-pensant. However, the matter is not so simple: we lack the true denominator of how many subjects who relapsed received chemotherapy to try to achieve a second complete remission but died en route to a transplant or achieved a second remission but did not proceed to a transplant for diverse reasons. As we shall see, these data are critical in determining whether it is better to transplant someone in second remission or in untreated or partially treated relapse.

Most comparisons of outcome transplants in individuals with AML in different disease states (first remission, second remission, relapse and so on) use data from the Center for Blood and Marrow Research (CIBMTR) and European Group for Blood and Marrow Transplantation (EBMT). However, drawing strategic conclusions from observational databases on a subject like this is inappropriate because these data sets include only transplant recipients, and not everyone who could have received a transplant. Clearly, this differs from an intent-to-treat analysis used in evaluating data from prospective trials. For example, if 100 individuals with recurrent AML could receive a transplant but centers transplant only 25 fit individuals in second remission, the data set will have data on these 25

and not the 75 who could receive a transplant but did not. Missing from the data set are: (1) individuals dying from therapy designed to achieve second remission; (2) persons achieving second remission but no longer fit for a transplant in someone's estimation (physicians understandably differ on this point); (3) transplant candidates lacking funds or insurance coverage (a variable correlated with many health-care outcomes[8]); and (4) others who might have received a transplant from transplant centers that use different selection criteria.

There are several possible solutions to this problem, none of which is easily accomplished. Developing a population-based observational data set of AML subjects from diagnosis regardless of therapy is one approach. Continued follow-up of subjects on randomized trials after completing their assigned therapy is another. Data from a recent large Medical Research Council (MRC) study that did precisely this are informative[9]. Many subjects who did not receive a transplant in first remission and relapsed achieved a second remission after receiving chemotherapy followed by a transplant, usually in second remission. Their outcome was remarkably good. However, there were several important unknowns including precisely why these subjects, many of whom had an HLA-identical sibling donor, declined a transplant in first remission. Might there have been selection biases or other confounders? Although unknown, these data suggest postponing a transplant in first remission in some individuals. There are two additional caveats to this type of analysis: (1) subjects entering these trials are unlike most individuals with AML in the United States where <10% of adults with AML enter clinical trials; and (2) confounding by biases influencing off-study interventions and follow-up[10,11].

Is a transplant the only effective therapy for relapse?

We also need to consider that some individuals with recurrent AML may achieve long-term survival with a second course of chemotherapy. For example, second remission rates exceed 50% in some individuals with favorable prognostic variables such as a first remission duration of 41.5 years, those with inv(16) and those without t(8:21)[12–16]. In the recent MRC study of 41000 subjects cited above, the 5-year leukemia-free survival was nearly 20%[9]. It is, of course, difficult to predict in early first remission which individuals who relapse will do well with reinduction chemotherapy, especially as duration of first remission is a key variable. But we can, at least, avoid the common fallacy that we need to transplant individuals in long first remission because time is running out.

We agree many individuals who relapse never get to a transplant. But some, even many, could receive a transplant without further therapy or with additional therapy aimed at disease control rather than receiving reinduction therapy. Importantly, there are no data from any intent-to-treat analysis showing a benefit of giving antileukemia drugs to individuals with recurrent AML headed for a transplant. For example, although some data suggest a correlation between percent of pretransplant myeloblasts and post-transplant survival that would favor giving pretransplant antileukemia therapy[17], this benefit may be offset by adversely affecting performance score and by loss of subjects who become transplant ineligible because of therapy-related complications. In addition, there is an obvious selection bias complicating interpretation of these data.

To determine the best strategy for individuals with AML in first remission and/or those who relapse, we need to know what was the outcome of all subjects, and not just those transplanted in second remission. Moreover, this outcome should be compared with results in these individuals had they received a transplant in first remission. Obviously, the correct answer cannot be accurately estimated from an observational database of transplant recipients. The few data we have from large clinical trials suggest no substantial difference in outcome of subjects with standard-risk AML who receive a transplant in first remission versus reserving transplants only in those who relapse[9]. However, even these data have statistical limitations such as post-randomization confounding by selection biases including subsequent therapy(ies) and loss to follow-up such that results of randomized clinical trials come to resemble those of observational databases[10]. In addition, as indicated, we do not know what selection biases operate, especially in individuals with an HLA-identical donor transplanted in second rather than in first remission. The bottom line is we lack an appropriate database to interrogate on the issue of best strategy.

Can we accurately predict which individuals with AML in first remission will relapse?

Another important issue is our inability to accurately predict on the subject level the relapse risk in an individual with AML in first remission. Most prognostic variables operate in the early phases of AML therapy, often before a transplant decision is made. Even under ideal circumstances, only part of the variance in outcomes in individuals with AML in first remission is explained by known variables. These variables are useful for defining outcome of a cohort but less so the outcome of an individual in whom we need to make a specific therapy recommendation. Because of the statistical approach used to define risk cohorts, it is axiomatic that a good- or standard-risk cohort will have a better outcome than a high-risk cohort. However, because confidence intervals of these groups often overlap, some individuals in the low-risk cohort may relapse, whereas some individuals in the high-risk cohort may not. This situation is unavoidable given our imprecision of prediction and considerable unexplained variance. For example, Walter et al.[18] recently addressed this question in a large setting of remission induction data set. The area under the receiver operating characteristic curve (ROC AUC) of their predictive model was B0.75, indicating the model performed better than chance (AUC ¼ 0.5) but was wrong in nearly one-half of cases. (A perfect model would have an AUC ¼ 1.0). No such ROC AUC analysis is reported from a large data set of individuals with AML in first remission eligible to receive a transplant. A net reclassification index analysis of this issue is not reported but is unlikely to perform better[19]. (Net reclassification index is another technique to evaluate the predictive value of a test). We consider this issue in greater detail in the next section.

Is minimal residual disease (MRD) testing the answer?

What of individuals with AML in first remission with so-called MRD? Is this a clear-cut reason to recommend a transplant in first remission? The answer is no. First, the term MRD is a relic of an earlier era. The test(s) used to detect residual leukemia cells and the cut point for declaring a test result positive need precise definition[20].

In addition, when the results of a test are handled as a binary (negative or positive) rather than expressed as a probability of correlating with relapse based on analysis of a ROC, it is unavoidable that some test results misclassify individuals with AML in first remission as to their relapse risk. Moreover, there is little or no consensus on the definition of MRD in individuals with AML. For example, in a recent carefully done study, individual who were 'MRD-positive' after consolidation chemotherapy had more than twice the relapse risk as individuals who were 'MRD-negative' (B70% percent vs B30%)[21]. However, we need to consider that one-third of subjects who were MRD positive did not relapse, and one-third of subjects who were 'MRD-negative' relapsed. Obviously, this prediction accuracy is not especially helpful in making therapy recommendations for individual subjects.

Several other considerations are as follows. (1) We do not know which cells we need to eliminate or whether we need to eliminate all leukemia cells to cure AML. Are the cells we detect by current MRD tests the target for leukemia eradication or is the target less-differentiated leukemia cells or even leukemia stem cells with a different phenotype and/or genotype than leukemia cells in the blood or bone marrow? (2) When numbers of residual leukemia cells in the body are low ($<10E^{-3}$) sampling error is more important than sensitivity of the assay in detecting MRD[22]. This is confounded by different frequencies of leukemia cells in blood versus bone marrow samples. (3) AML exhibits substantial clonal complexity. Often leukemia clones (or subclones) detected at relapse have a different genotype and/or phenotype than cells detected at diagnosis[23]. (4) Phenotypes and even genotypes of leukemia and normal cells may have considerable overlap. (5) Finally, MRD assays are not standardized. If you doubt the limitations of using MRD testing data to direct therapy of individuals with AML, consider the complexity of using MRD test data to direct therapy of CML in a situation with a more sensitive and specific MRD test[24,25].

Because of these limitations, we think using data from MRD testing to determine whether to do a transplant in first remission is flawed and presently of limited value to the physician who needs to make a therapy recommendation in a specific individual, and not a cohort. For example, in the only prospective study of MRD in young individuals with AML

using multiparameter flow cytometry and a binary MRD test cut point of $10E^{-2}$, MRD testing was informative regarding a transplant decision in <20% of the starting cohort[22]. We are left wondering how to handle the remaining 80%. Most importantly, we lack data from any prospective study showing a better outcome when individuals with MRD in first remission are assigned to a transplant versus chemotherapy. Finally, we need to recall that a higher relapse rate in individuals with MRD is again a self-fulfilling prophesy; although many individuals with MRD relapse, other do not. They are more interesting and problematic when one considers advising them to receive a therapy with a high therapy-related mortality.

These considerations lead to the axiom: the best predictor of relapse is relapse. Everything else is a surrogate with unavoidable false-positive and -negative rates. The only disadvantage of using relapse to trigger a transplant decision is if the outcome of transplants is compromised by waiting for relapse in precisely the same subjects. This is the argument of those favoring transplants in first remission but we are not convinced. No prospective study has shown a benefit, whereas the advantages of waiting for relapse are clear: no unneeded transplants and no individuals cured by chemotherapy will die from a transplant. This is a powerful argument, especially to the physician advising an individual with AML in first remission where the risk of an iatrogenic death in someone possibly already cured by chemotherapy carries greater weight than a disease-related death (primum no nocere). Every physician appreciates this important distinction; statisticians who deal with cohorts of subjects may not. And although some have argued the best predictor of second remission is second remission, this misses the point as individuals with recurrent AML other than only those in second remission also benefit from a transplant, perhaps to the same overall magnitude (see above).

The calculus for determining appropriateness of any medical intervention requires evaluating benefit versus risk in each individual. Here, appropriateness means the anticipated benefit of an intervention should exceed the anticipated risk by a sufficient margin such that the intervention should be performed[26]. This decision can be informed by data from clinical trials, observational databases and/or structured quantification of expert opinion but subject-level data are often lacking. Moreover, deciding if a transplant in first remission is appropriate requires consideration of age, gender, pretransplant conditioning regimen, genetic relatedness between donor and recipient and other variables. In addition, there is continued development of new transplant techniques and advances in supportive care, some of which could improve outcomes of transplants in individuals with recurrent AML. New types of post-relapse therapy such as using chimeric antigen receptor T-cells, new transplant conditioning regimens such as use of radiolabeled bone marrow seeking monoclonal antibodies and new post-transplant therapies to increase a putative graft-versus-leukemia effect may favorably alter outcomes of transplants in individuals who relapse but are not in second remission[27–29]. As we discussed, it may also be possible to accurately predict relapse earlier in individuals in first remission using molecular and/or immunological techniques but we are not there yet in typical AML.

Finally, there is the important input of an individual's objectives and risk tolerance: some of us are arm chair adventurers whereas others are sky divers or ice climbers. Some people want to live long enough to celebrate a next Christmas; others will bet all on a small chance of cure.

We appreciate transplants can improve likelihood of long-term survival in some, perhaps many, individuals with AML. We also realize the need to make therapy-related recommendations based on available data. Nevertheless, we think current data are inconclusive as to whether individuals with standard- or high-risk AML should have a transplant in first remission. We also want to disarm the myths that only individuals who relapse and achieve second remission benefit from a transplant, that everyone with AML who relapse should receive reinduction chemotherapy, that everyone with AML who relapse are incurable unless they receive a transplant and that we can accurately predict, on the subject level, which individuals in first remission will relapse. We are not therapy nihilists. However, more work is needed on these complex issues as is collecting data permitting definitive conclusions regarding the best therapy strategy for individuals with AML in first remission and in those who relapse. Randomized

trials of alternative strategies are also needed.

We realize we are fighting an uphill battle with some of our ideas. Experimental psychologists and brain researchers are familiar with the Einstellung effect or heuristic similar to confirmation bias whereby experts tend to stick with the solution to a problem or dilemma that comes first to mind and ignore alternatives including some that are better or more efficient. Amidst a rising tide of enthusiasm for transplants in AML in first remission, we hope not to be judged like Socrates at his trial: 'Incessant, irksome, irritating questioning of all aspects of existence as a deliberate perversity.' Importantly, we hope our survival probability is better than his.

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Conflict of interest

RPG is a part-time employee of Celgene Corp. PHW is a speaker for Celgene Corp., Novartis and Janssen. HML is a consultant to Actinium Pharmaceuticals, Inc. and Pluristem Therapeutics, Inc. and a speaker for Celgene Corp. Dr Charles Schiffer claims he recently heard Galen comment on his remedy.

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