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Incorporating Measurable (“Minimal”) Residual Disease-Directed Treatment Strategies to Optimize Outcomes in Adults with Acute Myeloid Leukemia

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Abstract

Curative-intent therapy leads to complete remissions in many adults with acute myeloid leukemia (AML), but relapse remains common. Numerous studies have unequivocally demonstrated that the persistence of measurable (“minimal”) residual disease (MRD) at the submicroscopic level during morphologic remission identifies patients at high risk of disease recurrence and short survival. This association has provided the impetus to customize anti-leukemia therapy based on MRD data, a strategy that is now routinely pursued in acute promyelocytic leukemia (APL). While it is currently uncertain whether this approach will improve outcomes in AML other than APL, randomized studies have validated MRD-based risk-stratified treatment algorithms in acute lymphoblastic leukemia. Here, we review the available studies examining MRD-directed therapy in AML, appraise their strengths and limitations, and discuss avenues for future investigation.

Keywords

Acute myeloid leukemia (AML); adult; measurable residual disease (MRD); prognosis; risk-directed therapy

INTRODUCTION

With contemporary therapies, many adults with acute myeloid leukemia (AML) will enter a morphologic complete remission (CR) [1,2]. However, at that time, patients may still harbor as many as $\sim 10^{10}$ – 10^{11} leukemic cells [3,4]. It is thus not surprising that relapse from

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POTENTIAL CONFLICT OF INTEREST

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morphologic CR remains common in AML. This observation has highlighted the fact that conventional evaluation of the bone marrow and peripheral blood by immunohistochemistry-assisted light microscopy lacks the sensitivity to detect a clinically relevant burden of AML cells. Over the last 2 decades, several methods have been developed to identify and quantify submicroscopic amounts of “minimal” (or, perhaps more appropriately coined, “measurable” [5]) residual disease (MRD) [6–12] that persist in morphologic CR. Measurements of MRD in AML are complicated by (1) the presence of preleukemic genetic lesions such as those seen in individuals with clonal hematopoiesis of indeterminate potential (e.g. mutations in *DNMT3A*, *TET2*, and *ASXL1*), (2) the genetic and molecular disease heterogeneity at initial AML presentation with evolution over the course of the illness, (3) the possibility that minor subclones can emerge at the time of recurrence, and (4) the persistence of some genetic abnormalities in patients in long-term clinical remission, likely because of the survival of preleukemic hematopoietic stem cells [13–19]. As a result, uncertainties persist in terms of optimal targets for MRD detection, assay platform (e.g. flow cytometry, quantitative polymerase chain reaction (qPCR), digital PCR, and/or next generation sequencing), the timing and frequency of measurements to best capture disease kinetics (increasing evidence indicates that repeated MRD measurements over the treatment course provide more useful information than single time point assessments [20,21]), thresholds to declare MRD positivity, and raw data analyses [9,10]. Furthermore, methodological approaches await harmonized across individual laboratories. Nevertheless, numerous studies have concordantly demonstrated that the presence of MRD after induction or consolidation therapy or around the time of hematopoietic cell transplantation (HCT) identifies patients at particularly high risk of disease recurrence and short survival even after adjustment for other risk factors such as baseline cytogenetics and/or mutational profiles [6,8,9,22]. These data have generated significant interest in more widespread incorporation of MRD into customized treatment strategies for patients with AML, e.g. to intensify therapy in patients with MRD^{pos} CR and/or to scale back potentially unnecessary therapy in patients without detectable MRD. Here, we will review available information pertaining to the use of MRD in personalized decision making for patients with AML, consider the strengths and limitations of these investigations, discuss ongoing studies that may guide clinical use of MRD, and suggest clinical trial opportunities to establish (or refute) the value of MRD-directed therapy in AML.

MRD-DIRECTED THERAPY: LESSONS LEARNED FROM ACUTE LYMPHOBLASTIC LEUKEMIA (ALL) AND ACUTE PROMYELOCYTIC LEUKEMIA (APL)

MRD-directed therapy to optimize treatment outcomes is not an unprecedented concept for patients with acute leukemia. Studies in ALL and APL support the validity of this strategy. In ALL, a disease in which levels of MRD are well established as an important, independent prognostic indicator during remission induction and consolidation, multiple non-randomized prospective trials have suggested better outcomes with MRD-guided treatment [23–26]. Two recent reports from the UKALL 2003 trial now also provide evidence from a randomized study that treatment reduction is feasible for patients predicted to have low-risk disease

based on MRD data, whereas augmentation of post-remission therapy can improve event-free survival in MRD-defined higher risk disease albeit at the cost of increased toxicity [27,28]. In APL, data from randomized trials do not exist, but several non-randomized studies suggest that preemptive therapy based on serial MRD monitoring can prevent frank relapse and associated bleeding complications and improve patient survival [29–31].

WHERE ARE WE WITH MRD-DIRECTED TREATMENT IN NON-APL AML?

While MRD data have repeatedly been shown to be very useful in the risk stratification of cohorts of AML patients [6,8,9,22], a recent analysis in adults with newly diagnosed *de novo* AML treated with intensive chemotherapy on the SWOG S0106 trial has indicated that MRD information at the time of remission achievement may improve the accuracy of survival prediction for individual patients only minimally [32]. This observation may caution against excessive reliance on MRD as a tool to dictate management in individual patients, at least when only measured at a single time point. Still, the recurrent demonstration of the relationship between MRD status and relapse risk in non-APL AML provides a strong rationale for the testing of MRD-based therapeutic strategies. To date, however, no data on the impact of MRD-directed therapy in AML exist from prospective randomized studies, but results have been reported from two prospective, non-randomized multicenter studies that have evaluated risk-directed approaches based on MRD status. The first study is the pediatric AML02 trial, which has used a combination of MRD measurements and genetic disease features to direct therapy decisions in 232 patients aged 2 days to 21.4 years with newly diagnosed *de novo* AML, therapy-related or myelodysplasia-related AML, or mixed-lineage leukemia [33]. The MRD status after the first induction course was used to intensify the timing of the second induction course and to add an additional agent (gemtuzumab ozogamicin), and was again used after induction 2, in combination with cytogenetics, to assign the intensity of the consolidation modality (allogeneic HCT vs. consolidation chemotherapy). An improvement in outcomes with this strategy was suggested when comparing results with previous treatment cohorts. However, because of patient heterogeneity and improving supportive care with substantially decreasing treatment-related mortality over time [34–36], comparisons with “historical” control groups can be problematic and results need to be interpreted cautiously. The second study is the AML05 trial, which examined 116 patients aged 15–60 years with t(8;21)(q22;q22) AML who achieved morphologic remission with 1–2 courses of induction therapy and then completed 2 cycles of intermediate-dose cytarabine-based consolidation therapy [37]. The lack of a major molecular response (MMR, defined as a >3 log reduction in *RUNX1-RUNX1T1* transcript levels from baseline) after the second course of consolidation, or loss of MMR within 6 months, was used to categorize patients into high- and low-risk. High-risk patients were recommended to proceed to myeloablative allogeneic HCT, whereas low-risk patients were advised to undergo 6 additional cycles of chemotherapy with the option of autologous HCT after 4 cycles. Only 69 patients (59%) were compliant with this risk-adapted approach and served as intervention group, whereas the other 47 patients were considered as non-risk adapted controls. Overall, the risk-adapted treatment approach resulted in survival outcomes similar to what has been reported earlier. In “as-treated” landmark analyses, allogeneic HCT was associated with lower relapse rates and better disease-free and overall survival as

compared to chemotherapy in high-risk patients. In contrast, low-risk patients did not significantly benefit from allogeneic HCT with regard to relapse risk and even experienced inferior disease-free and overall survival compared to those treated with chemotherapy/autologous HCT because of higher treatment related mortality [37]. This study may start to influence decision-making for post-remission therapy in patients with core-binding factor leukemia [38] and, by extrapolation, perhaps those with *NPM1*-mutated leukemia [39]. As a non-randomized investigation, however, this study introduces the possibility of significant biases, most importantly because we lack details as to how individual decisions to pursue/not pursue risk-directed therapy were reached. Accrual has been completed but no results are yet available from a third study, LAM07 (NCT01041040). This multicenter uncontrolled cohort study conducted by the Programa Español de Tratamiento en Hematología (PETHEMA) Foundation stratified patients before the first consolidation cycle according to genetic and molecular features as well as MRD status at the completion of induction therapy. Similar to the pediatric AML02 study, gemtuzumab ozogamicin was added to consolidation chemotherapy for a subset of intermediate- and high-risk patients as a means of treatment tailoring.

These multicenter studies are complemented by at least 2 single center studies in which preemptive therapy was given to MRD^{POS} patients to prevent frank disease relapse. In the prospective RELapse prevention with AZAcitidine (RELAZA) trial [40], four cycles of azacitidine were given to 20 of 59 screened patients with AML or myelodysplastic syndrome (MDS) in whom a decrease of CD34+ donor cell chimerisms to <80% was measured after allogeneic HCT. In 16 of these patients, donor chimerisms either increased or stabilized. Although relapses were eventually documented in 13 patients, it was felt that azacitidine could prevent or delay frank hematologic relapse in many patients [40]. A multicenter phase 2 follow-up trial is currently ongoing (RELAZA2, NCT01462578). In the second retrospective study, azacitidine was given to 10 patients with cytogenetically normal AML with *NPM1* mutation who had persistently detectable molecular MRD after completion of intensive chemotherapy, autologous, or allogeneic HCT [41]. A decrease of MRD levels 1 log was noted in 7 of the treated patients, and only 3 of the 10 patients experienced a frank relapse after a median follow-up time of 10 months. The results from both reports need to be interpreted very cautiously not only because of the uncontrolled nature of the studies but also because of the choice of primary endpoint. Even if relapses can be delayed or avoided in some patients, pre-emptive therapy may not necessarily lead to better survival because a subset of patients who do not undergo pre-emptive therapy and experience frank disease recurrence can be salvaged successfully with chemotherapy and/or allogeneic HCT. Moreover, pre-emptive therapies have associated toxicities, and their impact on quality of life will need to be carefully considered as well.

WHERE SHOULD WE GO WITH MRD-DIRECTED THERAPY OF NON-APL AML?

While all studies discussed above report provocative findings, their inherent short-comings limit the conclusions that can be drawn, and they should not be considered firm evidence that risk-adapted approaches to treatment escalation or de-escalation lead to better outcomes

in non-APL AML. Rather, they should provide the impetus to conduct well-designed and controlled studies with sufficient power and adequate follow-up time to generate compelling data that clarify whether/how MRD information is best used clinically to guide therapeutic decisions and improve treatment results for these patients. Several investigations with this primary objective are currently underway in non-APL AML. One important example is the AML17 trial, a prospective, randomized study conducted by the United Kingdom's AML Working Group of the National Cancer Research Institute (NCRI). In this trial, patients are randomized to a strategy of either MRD monitoring or not to assess its impact on survival, quality of life, and resource utilization, with resultant intervention(s) left up to the discretion of the treating physician. While the lack of standardized intervention may limit conclusions that can be drawn from this study, we expect that this trial will establish the feasibility of conducting a randomized investigation of this nature, and the results may help to illuminate the utility of MRD-based prescribing overall. Another example is the Gruppo Italiano Malattie EMatologiche dell'Adulto (GIMEMA) AML1310 trial, an ongoing non-randomized risk-adapted therapy study of adults ≥ 60 years of age with AML (NCT01452646) [42]. In AML1310, patients are risk stratified based on disease features at diagnosis. After the first cycle of consolidation therapy, low-risk patients undergo autologous HCT, whereas high-risk patients are offered allogeneic HCT regardless of the availability of an HLA-identical sibling donor. In contrast, intermediate-risk patients are assigned to autologous or allogeneic HCT dependent on the MRD status determined by flow cytometry following consolidation. As a potential limitation of this study, comparisons will be made to a historical rather than randomized control group.

There are several opportunities for MRD-based treatment intervention in AML. One logical possibility would be MRD-based treatment allocation at an early treatment time point, such as after completion of the first course of induction chemotherapy. Several studies have demonstrated that patients entering an MRD^{neg} CR early, i.e. with one cycle of standard induction chemotherapy, have a substantially lower relapse risk and live longer than other similarly-treated patients [43]. Possible strategies to augment subsequent therapy for MRD^{pos} patients could include the intensification of post-remission therapy cycles (e.g. through escalation of doses of standard anti-AML chemotherapeutics and/or addition of conventional chemotherapy drugs) and/or inclusion of investigational drugs such as small molecule inhibitors or targeted immunotherapeutics, the administration of additional post-remission chemotherapy cycles, the introduction of some form of maintenance therapy, or allocation to (intensified) HCT. Testing of investigational agents at this early time point during curative-intent therapy could offer an attractive therapeutic strategy in this situation that might improve outcomes and, at the same time, facilitate clinical drug testing. Numerous novel agents are being preclinically and clinically developed, many of which have presumed mechanisms of action that are distinct from those of conventional cytotoxic drugs (e.g. small molecule drugs inhibiting products from gene-mutated genes, bispecific antibodies, adoptive immunotherapies with gene-modified immune effector cells). Supported by recent clinical data in ALL [44,45], this allows optimism that some of the current investigational drugs could be effective in patients who remain MRD^{pos} after receipt of conventional AML therapy. Although the most meaningful endpoint for such an MRD-directed intervention will need to be defined empirically, we posit that achievement of an

MRD^{neg} state (rather than a simple numeric reduction in the amount of detectable MRD) may be more likely to translate into clinical benefit. Conversely, it is conceivable that some patients who would typically be considered candidates for allogeneic HCT based on cytogenetic/molecular risk but who achieve an early MRD^{neg} CR could derive similar or better outcomes from de-escalated treatment strategies such as post-remission therapy that is based on chemotherapy only or that includes autologous HCT. Alternatively, post-remission therapy could be de-intensified by reducing the number of consolidation courses administered, or by decreasing the drug doses used during these treatment cycles.

A second time point for MRD-based treatment intervention could be after the second course of induction chemotherapy in regimens that are based on double induction therapies. In the absence of known achievement of an early MRD^{neg} state (i.e. after the first induction course), the generally high relapse risk in non-APL AML may render chemotherapy de-escalation strategies for MRD^{neg} patients less attractive than maneuvers that aim to increase treatment intensity and/or introduce novel drugs for MRD^{pos} patients. Likewise, at any time point during or after completion of post-remission therapy, MRD-based treatment allocation should focus on the testing of intensified treatment strategies and/or novel agents for patients with persistent MRD. For patients slated to undergo HCT, augmentation of conditioning regimens (e.g. use of radiolabeled antibodies to maximize the dose of radiation to sites harboring leukemia cells), minimization of immunosuppression, and pre-emptive use of anti-leukemic or immunomodulatory agents could be tested to intensify allogeneic HCT if pre- or post-transplant MRD is detected. On the other hand, strategies based on autologous HCT or reduced-intensity allogeneic HCT could be exploited in patients presenting in MRD^{neg} CR for HCT, perhaps in particular if CR was achieved with the first cycle of chemotherapy [46].

In all investigations of MRD-directed therapy, the inclusion of appropriate control cohorts for comparison with appropriate observation periods will be essential. At its core, persistence of MRD is an indicator for the reduced sensitivity of leukemia cells to prior therapies. The presence of residual disease could thus simply mark those patients who are unlikely to be cured with subsequent similar-type therapies, even if disease levels are brought temporarily below the level of detection. Thus, while conversion from MRD positivity to MRD negativity is a reasonable immediate therapeutic goal, studies will need to assess carefully whether achievement of an MRD^{neg} state is indeed associated with improved longer-term outcomes. Moreover, additional therapy to reduce the tumor burden in patients with MRD is associated with a risk of complications such as organ toxicities or infections that could delay or prevent subsequent treatments including transplantation, increase treatment-related mortality, and offset any potential benefit of apparent immediate improvement in disease control.

CONCLUSION

Undoubtedly, the technical and logistical challenges surrounding MRD detection and monitoring have presented a major barrier to the development of randomized clinical trials of MRD-directed therapies in non-APL AML. So far, no single approach for the quantification of MRD has emerged as clearly superior, and several assay platforms continue to be explored clinically, each of which has specific advantages and disadvantages. For

example, flow cytometry-based methods to identify bulk or immature cell populations with abnormal immunophenotypes can be applicable to approximately 90% of patients with AML. On the other hand, they do require great technical expertise that is not universally available, and flow cytometry-based MRD assays have neither uniform sensitivity across all cases nor the exquisite sensitivity that can be achieved using optimized PCR-based methods. In contrast, monitoring of burdens of individual fusion genes (e.g. *RUNX1-RUNX1T1* or *CBFB-MYH11*) or mutations (e.g. *NPM1*) is feasible with great accuracy and sensitivity and has proven prognostically highly informative [38,47–49]. If individual fusion genes or mutations are measured, however, the latter methods may either fail to accurately measure clearance of AML cells or only be useful for defined, small subsets of patients. The monitoring of defined panels of frequently mutated genes, rather than individual genetic lesions, may be one approach to overcome the latter limitation and cover a much larger proportion of AML patients [12,50–52]. Clearance of molecular abnormalities in assays that are based on whole-genome or exome sequencing may provide an alternative strategy that can measure MRD more generally in AML patients with high sensitivity [53]. It is likely that such assays will soon be tested for the monitoring of MRD of AML patients more routinely. Work, in particular by the European LeukemiaNet, is ongoing to harmonize MRD assays, and tools to facilitate this process are being developed [54,55]. Hopefully, these efforts will lead to better quality data on which to base implementation of MRD assessments in clinical practice. In addition, refinement and standardization of MRD platforms and resulting data may render MRD-based surrogate endpoints (e.g. early MRD^{neg} CR) for drug testing more acceptable to regulatory authorities. Once validated that they are meaningfully related to conventional endpoints such as (event-free) survival or quality of life, such surrogate endpoints would shorten the time required for drug testing and expedite the introduction of new, better therapeutic strategies. These advances would complement efforts to test MRD-directed strategies in the clinic and, together, inform the use of MRD as biomarker to risk-stratify individual patients with non-APL AML and tailor their therapy.

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