Cross-sectional physician survey on the use of minimal residual disease testing in the management of pediatric and adult patients with acute lymphoblastic leukemia

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ABSTRACT

Objectives: Minimal residual disease (MRD) is a strong prognostic factor in acute lymphoblastic leukemia (ALL), which progresses quickly and is fatal within months if untreated. This study explored use of MRD testing in adult and pediatric B-cell ALL patients, and academic versus community settings.

Methods: A survey was administered to US-based hematologists/oncologists currently managing ≥5 B-cell ALL patients and using MRD tests. Descriptive analyses (frequencies and percentages) and Pearson's chi square testing assessed any differences in various characteristics.

Results: 150 adult treaters (treating physicians: 100 community, 50 academic) and 30 pediatric treaters participated. Use of MRD testing was higher among pediatric treaters (93% of patients) than adult treaters (73% of patients) (p<0.05), and higher among adult treaters at academic centers than in community settings (84% and 67% of patients, respectively; p<0.01). MRD testing is part of a standard protocol for 93% of pediatric treaters versus 53% of adult treaters. Pediatric treaters most commonly administer an MRD test during/after induction or upon relapse. No consensus on timing among adult treaters was noted.

Discussion: MRD testing is an important tool in the prediction of relapse in ALL. Resolving barriers could improve detection of molecular relapse in patients with ALL, particularly among adults and in community settings.

Conclusion: MRD testing is fairly common in treatment of ALL, but some barriers still exist in access.

KEYWORDS

B-cell acute lymphoblastic leukemia; minimal residual disease; flow cytometry; polymerase chain reaction

Introduction

Each year in the United States (US), there are approximately 5,970 new cases of acute lymphocytic leukemia (ALL), including both adult and pediatric patients, with approximately 1,440 deaths [1]. ALL generally progresses rapidly if untreated and can lead to death within months; thus, it is important to begin treatment soon after diagnosis [2]. The causes of ALL are multifactorial, with risk factors including exposure to high doses of radiation, previous experience of radiation therapy or chemotherapy, and genetic disorders [2].

Treatment success varies dramatically by age. Approximately 80–90% of adults will experience remission during treatment, with approximately 50% experiencing relapse [3]. Approximately 80% of ALL deaths occur in adults [4], despite only 40% of cases occurring in adults. Treatment success rates are higher among pediatric patients, with 80% achieving and remaining in remission. Among pediatric acute leukemias, ALL is the most common and accounts for 75–80% [2].

Minimal residual disease (MRD) testing has become a common practice during and following treatment for detecting leukemic cells below detection limits for morphologic complete remission (<5% blast in bone marrow). Presence of MRD is evidence of residual malignant leukemic cells in bone marrow and incomplete response to anti-leukemia therapy. Detection of MRD is associated with shorter event-free and overall survival compared to patients without MRD presence [5]. The National Comprehensive Cancer Network (NCCN) released official guidelines [6] about the necessity for monitoring MRD levels for ALL patients in complete remission. NCCN provides treatment options for patients with persistent MRD, including but not limited to blinatumomab, allogeneic stem cell transplant, and multi-agent chemotherapy. The most common techniques for MRD testing include multicolor flow cytometry, real-time quantitative polymerase chain reaction, and next-generation sequencing.
Although the practice and necessity of MRD testing is known, it is less clear how commonly and in what settings MRD testing is assessed with ALL patients in the US. This study’s objective was to explore what factors influence use of MRD testing by physicians from academic and community settings treating adult B-cell ALL patients, as well as by physicians primarily treating pediatric B-cell ALL patients.

Materials and methods
The study comprised a large-scale online administration of a quantitative, cross-sectional survey with US-based oncologists and/or hematologists who treat ALL patients and conduct MRD testing. Centralized ethics review board approval was obtained from Quorum Review (QR#32135) prior to the start of the study.

Recruitment
Participants were recruited, via a third-party recruitment agency, from a national database of physicians who had opted to participate in qualitative and quantitative panel studies. Interested physicians were supplied with a letter outlining the study’s purpose and participation requirements as well as a single URL to access the screener, consent form, and survey, which were programed and hosted on Conﬁrm it Survey Software version 19 (Conﬁrm it AS, London, UK).

Physicians who followed the URL first completed a self-reported eligibility screener. Participants were practicing oncologists or hematologists for ≥2 to <35 years, US board certiﬁed, working in either an academic or community practice, spending ≥60% of their time in direct care, actively monitoring or treating ≥5 B-cell ALL patients during the study, and utilizing MRD testing with any of their B-cell ALL patients. Physicians were considered ineligible if they currently practiced medicine in Vermont or at a government or VA hospital, due to inability to accept compensation, or had family or household members afﬁliated with a pharmaceutical company, healthcare company, or government agency in any research capacity, due to potential conﬂict of interest.

Eligible physicians provided consent via a one-page electronic consent form with information about the study, conﬁdentiality, and rights to withdraw without penalty. Physicians who were ineligible, based on screening or non-consent, were not allowed to continue to the main survey, and only screening data were collected from those physicians. A total of 150–200 completed surveys were targeted, with approximately 100 community-based physicians treating adult ALL patients, 50 academic-based physicians treating adult ALL patients, and 30 physicians treating pediatric ALL. Among the physicians treating pediatric ALL, 20 academic and 10 community treaters were targeted to have a broad sampling of physicians across different settings and demographics.

Study instrument
A survey was developed to explore the research questions, and its content was reﬁned during two rounds of pilot testing with physicians. The ﬁrst round involved qualitative interviews with physicians to determine whether the initial, paper-based version of the survey was comprehensive, comprehensible, and appropriate to the key research questions. In the second round, physicians completed the survey online while a moderator from the research team observed the length of time to complete the survey and whether there were any usability issues. Final adjustments were made to the online survey after completion of pilot testing and before survey administration in the quantitative phase.

The 30-item survey employed several types of questions to gather data on physician attitudes towards MRD testing. It was expected to take about 20 minutes to complete and comprised three sections: frequency of MRD testing, use of MRD testing, and future of MRD testing. Response scales included pre-deﬁned answer choices (both ‘choose only one’ and ‘choose all that apply’), rankings, and open-ended numerical or written responses. Survey choices were automatically saved, allowing participants to stop and continue at a later time.

Data analysis
For questions with pre-deﬁned categorical answers, results were described as the number and percentage of participants selecting each category, with missing data excluded from percentage calculations. For questions with open-ended numerical responses, results were summarized as the mean, standard deviation (SD), median, and range to describe the distribution of responses. For open-ended written responses, similar concepts were grouped into categories and described as the number and percentage of participants endorsing the category.

Descriptive analyses (number, percent, means, SD as appropriate) were conducted based on responses to items that asked treaters about MRD testing frequency, reasons for conducting MRD tests, the extent to which they agreed or disagreed with statements about beliefs related to MRD testing, and barriers to use of MRD testing. For questions wherein treaters were asked to rank their agreement with statements on a seven-point numeric rating scale, a choice of 6 or 7 was considered agreement with the statement, 1 or 2 was considered disagreement, and 3–5 were considered neutral. An exercise selecting and ranking the three most important statements from a pre-generated list
about how the nature and role of MRD testing in B-cell ALL will change in the next five years was descriptively analyzed.

Analyses of survey responses were performed separately for participants who treat a percent majority of pediatric ALL patients (≤17 years of age) and those who treat a percent majority of adults (≥18 years of age); this was determined by participants’ self-report. For the purpose of reporting, participants will be referred to as ‘adult treaters’ and ‘pediatric treaters.’ Furthermore, analyses were stratified for adult treaters by self-reported practice setting (i.e. academic versus community-based cancer center/hospital). Pearson’s chi square test was used to assess differences by adult-treater practice setting (academic versus community) and by primary patient population (adult versus pediatric).

Results

Sample description

A total of 180 physicians completed the quantitative survey. Of the 8,252 physicians who were initially invited to participate, 366 physicians initiated the self-screener (4.4%), with 186 physicians screening out due to ineligibility (51%), before participation targets were reached and the survey was closed to additional respondents. The majority of physicians were ineligible due to low volume of B-cell ALL patients in their practices, lack of appropriate board certification, and not having used any MRD testing in their practices (Supplementary Table 1).

Of the 180 participants, 150 were considered adult treaters, as their patients consisted of >50% adults. Adult treaters had practiced medicine for a mean of 12.7 years (SD = 7.1). The majority worked in community settings (n = 100, 67%) as opposed to academic settings (n = 50, 33%). Of the community treaters, most were affiliated with non-teaching hospitals (n = 59, 59%) and worked in a group practice of 6–20 physicians (n = 56, 56%). The median number of B-cell ALL patients currently treated by adult treaters, excluding outliers, was 20 (range = 5–284). Flow cytometry was the most common MRD test used (n = 82, 55%) (Supplementary Figure 1).

Thirty participants were considered pediatric treaters, as their patients consisted of >50% pediatric patients with ALL. Pediatric treaters had practiced medicine for a mean of 14.9 years (SD = 9.6). Ten (33%) of the pediatric treaters worked in community settings, while 20 (67%) worked in academic settings. Pediatric treaters who practiced in community settings were evenly split between non-teaching and teaching hospital affiliation (n = 5, 50%, respectively), and 5 (50%) pediatric treaters worked in group practices of ≤5 physicians. The median number of B-cell ALL patients currently treated by pediatric treaters, excluding outliers, was 30 (range = 5–350).

Survey results

MRD testing frequency, reasons, and beliefs (adult treaters)

Adult treaters reported testing 73% of their patients at some point during disease management. About half (n = 80, 53%) reported following a standard protocol or pathway for MRD testing. Common reasons reported in open-ended responses for why patients did not receive MRD testing were related to patient preference (n = 16/101, 16%), lack of insurance coverage for MRD testing (n = 13/101, 13%), poor availability/lack of inclusion in guidelines (n = 13/101, 13%), and cost to patients (n = 9/101, 9%) (Note: Not all physicians provided a response to this question).

Adult treaters reported testing for MRD in the largest percentage of patients immediately after completion of induction (in 59% of patients) or consolidation therapy (in 52% of patients). When stratified by type of practice, academic treaters and community treaters both reported testing the largest percentage of patients immediately after completion of induction (in 73% and 52% of patients, respectively) or consolidation therapy (in 64% and 46% of patients, respectively) (Figure 1).

Adult treaters who ranked their top three reasons for assessing MRD reported that they often conduct MRD testing to determine stem cell transplant eligibility (n = 64, 43%), provide information on prognosis after induction (n = 61, 41%) or consolidation (n = 42, 28%), or detect disease recurrence (n = 42, 28%) (Figure 2).

Adult treaters were asked the extent to which they agreed or disagreed with statements about testing attitudes and beliefs on a seven-point numeric rating scale. They often agreed (n = 60, 40%) rated a 6 or 7 that patients with MRD-positive histories were tested more frequently. Most agreed that MRD positivity was a marker of poor prognosis (n = 88, 59%) and that MRD testing would confirm treatment success or remission (n = 89, 59%), and were neutral about whether MRD would inform next steps for treatment (n = 77, 51%). Slightly more adult treaters disagreed with a statement indicating that MRD testing was unclear for adult patients due to lack of robust data (n = 29, 19%) than agreed (n = 25, 17%) (Figure 3).

When stratified by practice, more academic treaters than community treaters (n = 16, 32% and n = 13, 13%, respectively) disagreed that MRD testing was unclear for adult patients due to lack of robust data. Conversely, more academic treaters than community treaters agreed that MRD positivity was a marker of poor prognosis (n = 35, 70% and n = 53, 53%, respectively; p-value = 0.046), that MRD testing would confirm treatment success or remission (n = 35, 70% and n = 54,
54%, respectively; \( p \)-value = 0.06), and that MRD testing would inform next steps for treatment (\( n = 32, 64\% \) and \( n = 37, 37\% \), respectively; \( p \)-value = 0.002) (Figure 4). Adult treaters who conduct MRD testing during remission following completion of front line therapy (\( n = 81, 54\% \)) were asked to indicate their reasons for doing so in an open-ended response. The most common reason was the indication of relapse by abnormal hematology results (academic treaters \( n = 18, 82\% \) and community treaters \( n = 40, 68\% \)), followed by patient report of symptoms that may indicate relapse (academic treaters \( n = 14, 64\% \) and community treaters \( n = 33, 56\% \)), and patient history of MRD positivity (academic treaters \( n = 14, 64\% \) and community treaters \( n = 28, 47\% \)). For the majority of adult treaters who provided data (\( n = 62 \)), frequency of MRD testing during remission was most often reported as once per three months (\( n = 24, 24\% \) or once per six months (\( n = 18, 18\% \)). Approximately 30% (\( n = 54 \)) do not test MRD for patients receiving treatment following

![Figure 1. Physician estimate of therapy phase when assessing MRD. % of patients; counts not mutually exclusive.](image1)

![Figure 2. Physician-ranked reasons for assessing MRD in patients with B-cell ALL among adult and pediatric treaters. % of physicians ranking reason in top 3. Data labels less than 7% are not shown, except for Total Rank %.)](image2)
relapse, with the most common reason being that MRD testing does not change their treatment management \((n = 14, 26\%)\).

**MRD testing frequency, reasons, and beliefs (pediatric treaters)**

Pediatric treaters reported testing 93% of their patients at some point during the management of their disease. Almost all \((n = 28, 93\%)\) reported following a standard protocol or pathway for MRD testing. Nineteen pediatric treaters \((63\%)\) reported administering MRD tests to all of their patients, and the eleven pediatric treaters \((37\%)\) who reported treating less than 100% of their patients were asked their reasons for not testing. Based on open-ended responses, reasons patients did not receive MRD testing were related to patient preference \((n = 2/11, 18\%)\), cost to patients \((n = 2/11, 18\%)\), poor availability and lack of inclusion in guidelines \((n = 1/11, 9\%)\), and lack of insurance coverage for MRD testing \((n = 1/11, 9\%)\).

Pediatric treaters reported testing for MRD in the largest percentage of patients immediately after completion of induction therapy \((84\%)\) and during or after treatment following relapse \((77\%)\) (Figure 1). Figure 2 shows the reasons that pediatric treaters often conduct MRD testing, while

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**Figure 3.** Physician agreement with MRD testing attitudes and beliefs among adult and pediatric treaters. % of physicians, 1–7 scale (1 'completely disagree'; 7 'completely agree'). Data labels less than 10% are not shown.

**Figure 4.** Physician agreement with MRD testing attitudes and beliefs among academic and community treaters. % of Physicians, 1–7 scale (1 'completely disagree'; 7 'completely agree'). Data labels less than 10% are not shown.
Figure 3 shows their agreement on statements related to MRD testing attitudes and beliefs; a vast majority of pediatric treaters (n = 23, 77%) agreed that MRD positivity is a marker of poor prognosis.

Pediatric treaters who conduct MRD testing during remission following completion of front line therapy (n = 5, 17%) most commonly wrote that relapse by abnormal hematology results was the reason for testing (n = 4/5, 80%). Three pediatric treaters (10%) wrote that they do not test MRD for patients receiving treatment following relapse due to disparate reasons, including cost (n = 1/3, 33%), that testing is protocol-specific (n = 1, 33%), or that the patient was already enrolled in a trial or study (n = 1/3, 33%).

**Barriers to increasing the frequency of minimal residual disease testing**

Overall, when asked to choose from a list of potential barriers affecting their decision to conduct MRD testing, adult treaters most often endorsed cost of testing (n = 62, 41%), insurance hurdles (n = 54, 36%), insufficient data to support more frequent MRD tests (n = 48, 32%), and access to testing (n = 45, 30%). The most frequently reported barriers for pediatric treaters also included insurance hurdles and insufficient data to support more frequent MRD tests (n = 11, 37% each). Twenty-nine adult treaters (19%) and eight pediatric treaters (27%) reported having no barriers to MRD testing (Figure 5).

The most frequent barriers for community treaters were cost (n = 50, 50%; academic treaters n = 12, 24%; p-value = 0.002) and insurance (n = 42, 42%; academic treaters n = 12, 24%; p-value = 0.03). Academic treaters most frequently reported insufficient data to support more frequent tests generally (n = 18, 36%; community treaters n = 30, 30%; p-value = 0.46) and insufficient data to support more frequent tests in certain patients (n = 13, 26%; community treaters n = 25, 25%; p-value = 0.89) as barriers that affected their MRD testing decision. Almost a third of academic treaters (n = 16, 32%) indicated having no barriers to MRD testing, as opposed to 13% (n = 13) of community treaters (p-value = 0.05) (Figure 5).

**Future of minimal residual disease testing**

Adult and pediatric treaters anticipated a broad range of roles for MRD testing, including identifying new treatment options (n = 76, 51% and n = 16, 53%, respectively); expanding knowledge in induction therapy (n = 60, 40% and n = 11, 37%, respectively); improving relapse predictions (n = 58, 39% and n = 14, 47%, respectively); improved tests that produce more accurate, reliable, and reproducible MRD results (n = 54, 36% and n = 10, 33%, respectively); and expanding knowledge in consolidation therapy (n = 52, 35% and n = 17, 57%, respectively) (Figure 6). ‘New treatment options will be indicated for patients with MRD positive disease’ was most frequently ranked most important in determining the nature and role of MRD testing in B-cell ALL in the next five years, by both adult and pediatric treaters (n = 31, 21% and n = 6, 20%, respectively).

That MRD testing in the future could lead to new treatment options was most frequently ranked first, second, or third most important by academic and community treaters (n = 28, 56% and n = 48, 48%, respectively). Academic adult treaters most frequently

![Figure 5. MRD test frequency barriers among adult, pediatric, academic, and community treaters. % of physicians.](image-url)
ranked the statement ‘Improved tests; more accurate, reliable and reproducible MRD results’ as the most important out of all of the statements provided (n = 12, 24%), whereas community adult treaters were more likely to rank ‘new treatment options will be indicated for patients with MRD positive disease’ as most important (n = 22, 22%).

Discussion

A total of 180 oncologists/hematologists who use MRD testing, 150 of whom treated primarily adults and 30 of whom treated primarily pediatric patients, were recruited to participate in a survey study assessing physician attitudes towards MRD testing frequency, reasons for testing, barriers to MRD testing, and the future of MRD testing in B-cell ALL. Overall, survey results showed that adult treaters were less likely to conduct frequent MRD tests than pediatric treaters. Adult treaters reported more barriers to MRD testing than pediatric treaters, with adult community treaters reporting the most barriers to MRD testing.

MRD is a direct measure of leukemic disease and is a strong risk factor for pending relapse. Research suggests better outcomes are achieved with an MRD-negative assessment [5], including longer event-free and overall survival. MRD-directed therapy is actively being explored with agents such as blinatumomab [7] which can convert patients with MRD to no MRD. Improvement in the completeness of regular MRD testing can generate more data on the success of various induction/consolidation therapies to achieving MRD negativity outside of clinical trial settings. Additionally, trials of several new therapies such as inotuzumab [7] and tisagenlecleucel [8] are evaluating MRD negativity as a secondary endpoint in addition to complete remission.

NCCN and the European Society for Medical Oncology (ESMO) both highly recommend that MRD testing be a mandatory part of post-induction follow-up care for appropriate risk stratification [6,9]. Conventional recommendations are for patients with persistent MRD to seek out allogeneic hematopoietic stem cell transplant (alloHSCT) [10]. A subset of patients undergoing alloHSCT with MRD can become MRD negative; however, undergoing alloHSCT in the presence of MRD has demonstrated a worse outcome compared to MRD negativity at time of transplant [10-12]. NCCN also offers MRD-directed therapy with blinatumomab as a treatment option [6].

The higher prevalence of MRD testing in pediatrics is unsurprising, as much of the research supporting the use of MRD testing was developed from the pediatric ALL groups. Studying timing of MRD assessment has found that consistent early and late monitoring is important in understanding and appropriately risk stratifying patients [13]. The Children’s Oncology Group, during early and late monitoring, has identified that the treatment intensification of therapy is important in altering relapse occurrence [14]. MRD testing identifies patients who may be particularly high risk and can identify potential treatment options, based on research by the Berlin-Frankfurt-Münster (BFM) group [15]. Additionally, there is additional need to further streamline and improve the speed of MRD testing [16].

This study showed that testing for MRD is relatively common within the sample but, among adults, is most often performed only once and consensus is lacking on the timing of when to test during treatment. Although MRD testing is usually performed only once or twice across age groups, serial measurement of MRD has shown that patients may become MRD negative at several points along the treatment pathway [11]. In
particular, patients who remain MRD negative after consolidation have significantly better outcomes than those who do eventually have MRD positivity [10,11]. As previously reported, MRD negativity prior to alloHSCT is associated with better overall outcomes [10-12], and a key finding from this study was that many physicians recognize MRD testing as a key decision point on proceeding to transplant. Understanding the importance of MRD negativity prior to transplant will become increasingly important to enable long, durable remission for increasing numbers of patients undergoing transplant over time [17].

Oncologists and/or hematologists reported conducting MRD tests more frequently among pediatric than adult ALL patients, reporting cost and lack of insurance coverage as common barriers. Therefore, changes in reimbursement and access will allow more consistent use of MRD testing among patients. Such changes could be brought about by new regulatory approvals that recognize the routine use of MRD testing in B-cell ALL.

Pediatric patients are often given more aggressive treatment, and nearly all pediatric treaters reported following standard pathways or protocols for MRD testing that more frequently test for MRD. As a result of more aggressive treatment compared to adult patients, a higher proportion of pediatric B-cell ALL patients receive more intensive regimens, are MRD negative after induction therapy, and undergo alloHSCT. In comparison, only half of adult treaters reported following a standard pathway or protocol, and adult treaters were more likely to cite lack of a protocol or robust data as reasons for not testing for MRD. Given the abundance of data showing improved outcomes of patients with MRD negativity, more outreach to demonstrate the benefits of attaining MRD negativity may be needed.

This study was limited by US-specific sampling and generalizability. All participants practiced medicine in the US, and attitudes to MRD testing as well as protocols directing the use of MRD testing may differ outside of the US. Oncologists and/or hematologists who did not perform MRD testing with any patients were excluded from the study (n = 31, 17%), limiting responses regarding why physicians may choose not to test for MRD. Approximately 20% of physicians were pediatric treaters (n = 30), and because this was a relatively smaller sample, the views represented by these treaters may not be as representative as the adult treaters (n = 150). However, as MRD testing in pediatrics has been a long-established practice, the practices described here are likely to be representative US-wide. Although screening criteria were applied with quotas to encourage a representative sample of physicians treating B-cell ALL, physicians were self-selected by opting in to the national database of physicians willing to participate in surveys. The high number of ALL patients seen by some physician respondents potentially indicates an over-sampling of this characteristic, and may not be reflective of experiences of oncologists/hematologists with fewer patients. Recall bias may be present, as several estimates come from physician self-report rather than chart reviews of patient data, but this is unlikely to be differential as physicians are unlikely to report results in a systematically biased manner.

MRD testing is an important tool for monitoring and assessing depth of therapy and risk of relapse for ALL patients in complete remission. Testing is more common and frequent among pediatric-treating academic physicians treating B-cell ALL patients, and relatively less common among adult-treating community physicians. Resolving barriers of cost and insurance, as well as greater inclusion in treatment protocols, could improve tracking when an ALL patient is in molecular relapse (but not yet in hematologic relapse). Improving MRD testing and tracking is most important among adults and in community clinic settings, as MRD testing is least commonly used in these settings. Additional understanding of MRD status will help better direct further advances in trying to improve ALL patient outcomes.

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