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RESEARCH ARTICLE

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Description and prognostic significance of the kinetics of minimal residual disease status in adults with acute lymphoblastic leukemia treated with HyperCVAD

Ryan D. Cassaday[1,2] | Philip A. Stevenson[3] | Brent L. Wood[4] | Pamela S. Becker[1,2] | Paul C. Hendrie[1] | Brenda M. Sandmaier[1,2] | Jerald L. Radich[1,2] | Andrei R. Shustov[1,2]

[1]Department of Medicine, University of Washington School of Medicine, Seattle, Washington; [2]Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, Washington; [3]Clinical Statistics Division, Fred Hutchinson Cancer Research Center, Seattle, Washington; [4]Department of Laboratory Medicine, University of Washington School of Medicine, Seattle, Washington

Correspondence
Ryan Cassaday, Seattle Cancer Care Alliance, 825 Eastlake Ave E, Mailstop G3200, Seattle, WA 98109.
Email: cassaday@uw.edu

Abstract

HyperCVAD is a commonly-used regimen for adults with newly-diagnosed acute lymphoblastic leukemia (ALL). However, relatively little is known about the application of minimal residual disease (MRD) detection with this treatment. To address this, we studied 142 adults with ALL treated with hyperCVAD over a 10-year period who had MRD assessed by either multiparameter flow cytometry or (for patients with Philadelphia chromosome positive ALL) reverse transcriptase polymerase chain reaction for the *BCR-ABL1* translocation. In a multivariate analysis, patients who achieved MRD negativity (MRD^{Neg}) at any point had significantly better overall survival (OS; hazard ratio [HR] 0.43; $P = .01$) and event-free survival (EFS; HR 0.27; $P < .01$). Of 121 patients with MRD assessed at various points within 90 days of starting hyperCVAD, 50% ($n = 61$) had achieved MRD^{Neg}. Among those that became MRD^{Neg}, the median time to MRD^{Neg} was 68 days. Time to MRD^{Neg} was significantly associated with EFS ($P = .009$), but not OS ($P = .19$), implying increasingly better EFS the earlier MRD^{Neg} is achieved. These data add to our understanding of MRD assessment during treatment with hyperCVAD, aide clinicians with predicting relapse risk, and provide additional historical data on which future clinical trials can be designed.

1 | INTRODUCTION

Minimal residual disease (MRD) is an established prognostic and predictive biomarker in acute lymphoblastic leukemia (ALL).[1] Its presence (MRD^{Pos}) or absence (MRD^{Neg}) at specific points during different treatment regimens can be used to risk-stratify patients, often with such impact that historical risk factors like white blood cell count (WBC) at diagnosis and cytogenetics are no longer important.[2–6] The prognostic impact of a rapid early response is also well described, though primarily in pediatric regimens. MRD^{Neg} at the end of a 4-week induction and following consolidation in a pediatric regimen can be used to de-intensify therapy on the basis of a very low risk of relapse.[7] Alternatively, MRD^{Pos} despite 16 weeks of therapy is associated with a very high risk of subsequent relapse in adults.[8,9] This risk can be ameliorated by allogeneic hematopoietic cell transplantation (HCT) while in morphologic remission. Therefore, not only is achieving MRD^{Neg} critical to the success of ALL therapy, but also the time it takes to achieve this response is also important.

HyperCVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with methotrexate and high-dose cytarabine) is among the most widely used regimens for adults with ALL.[10] It has proven to be an effective backbone for the addition of novel targeted agents, including *ABL1* tyrosine kinase inhibitors (TKIs) for Philadelphia chromosome positive (Ph+) ALL[11–13] and rituximab for CD20+ disease.[14] However, because of its relatively unique schedule of administration (ie, 2 alternating cycles of therapy repeated up to 4 times), it is difficult to extrapolate methods of risk stratification by MRD identified in other regimens. Investigators from MD Anderson Cancer Center (MDACC) have begun to explore the impact of MRD status in the context of this regimen. Achieving MRD^{Neg} by 3 months of treatment initiation with hyperCVAD + TKI is associated with improved survival of patients with Ph+ ALL (as measured by reverse transcriptase polymerase chain reaction [RT-PCR] for *BCR-ABL1*), with persistence beyond 3 months leading to an increased risk of relapse and death.[15,16] Further, absence of MRD by multi-parameter flow cytometry (MFC) has been shown to have prognostic significance when assessed at the time of morphologic complete remission (CR) and at 3 and 6 months of treatment.[17] While these reports provide some suggestions regarding the application of MRD detection, they represent somewhat arbitrary time points in the experience from only one center. Thus, much remains to be understood regarding MRD assessments in the context of hyperCVAD.

Using our center's experience, we sought to better understand the role of MRD assessments during treatment with hyperCVAD. We hypothesized that not only achieving MRD^{Neg}, but doing so at an earlier time during treatment would be associated with better outcomes. If confirmed, this could provide useful information for the routine clinical use of hyperCVAD in adults with ALL, as well as potential surrogate endpoints for success with the testing of novel approaches for this very challenging disease.

2 | METHODS

2.1 | Patient selection

Records from consecutive patients older than 18 years with ALL who received care at our center between January 2005 and December 2014 were reviewed. Only patients that received hyperCVAD as initial therapy were included. Patients with isolated extramedullary disease (eg, lymphoblastic lymphoma without bone marrow involvement, isolated central nervous system disease) or Burkitt lymphoma/leukemia were excluded. All patients who were treated on an investigational study provided informed consent in accordance with the Declaration of Helsinki. Separate institutional approval was obtained for this analysis to retrospectively gather data from patient records and databases.

2.2 | Clinical data collection and definitions

Clinical characteristics of initial presentation and treatment rendered were reviewed from all patients. Only patients from whom sufficient data regarding remission status were available were included. High-risk clinical features were defined as age at diagnosis of $\geq$ 35 years, high WBC at diagnosis ($>$30,000/μL for precursor B-cell ALL, $>$100,000/μL for T-cell ALL), and adverse cytogenetics identified either by metaphase analysis or fluorescence *in situ* hybridization (FISH). Specifically, the following abnormalities were defined as high-risk, as reported previously: t(9;22) or Ph+; rearrangements involving *MLL* on 11q23; complex karyotype (ie, 5 or more structural or numerical abnormalities), low hypodiploidy, near triploidy, monosomy 7, and trisomy 8.[18–20] Decisions regarding the specifics of treatment and referral for allogeneic HCT were not prospectively assigned and were left to the discretion of the treating physicians.

2.3 | Definition of response assessments and MRD

All response assessments were based on evaluation of bone marrow examinations. The timing and nature of response assessments were left to the discretion of the treating physicians. MRD^{Neg} was defined as no evidence of quantifiably detectable disease by MFC and/or RT-PCR, provided any other measures utilized (ie, morphology, cytogenetics, and/or FISH) also did not detect signs of residual disease. Though these assays were not all uniformly applied to all assessments, MFC was used in all patients. The 9- to 10-color MFC platform used in our laboratory at the University of Washington (UW) has a sensitivity of 0.01%-0.001%.[21] However, MFC data from other laboratories were included when utilized, the operating characteristics of which are not immediately available. For the purposes of this analysis, "quantifiably detectable" was defined as the presence of sufficient abnormal signal such that an unequivocal numerical result was given in the clinical report. Results that were deemed by the interpreting pathologist to be "indeterminate," "below the threshold of enumeration," or the like were considered negative. Because of the high risk of morphologic relapse associated with recurrence of MRD,[22] relapse was defined as either morphologic (ie, $>$ 5% bone marrow blasts) recurrence or MRD reappearance,[23] except when MRD reappearance occurred transiently within the first 3 months after HCT.

2.4 | Statistical analysis

Frequencies of characteristics between groups were compared using a two-tailed Fisher exact test. Kaplan-Meier curves estimated the probabilities of overall (OS) and event-free survival (EFS). Events were defined as morphologic or MRD reappearance, change in treatment due to inadequate response, death from any cause, or secondary malignancy. Frequencies of characteristics were compared between groups using a Fisher's exact test. Cox proportional hazards models were used to investigate associations between variables. Further, a test of proportional hazards was used to assess the impact of time on the association between MRD and both OS and EFS, in which MRD was modeled as a time-dependent covariate with left-truncation. Left-truncation was used to account for the varying times at which patients were first assessed for MRD.[24] The results of this assessment were used to generate a smoothed beta plot, where beta represents the log of the hazard of an event if MRD^{Neg} is achieved with respect to the time at which MRD^{Neg} is observed (ie, if beta $<$ 0, then hazard is reduced).

3 | RESULTS

3.1 | Patient and treatment characteristics

From 241 adults with ALL treated at our center, we identified 144 (60%) that received hyperCVAD as their initial therapy. Two of these patients (1%) were excluded: 1 did not undergo any MRD assessments, and 1 had insufficient records available to know their outcome. The characteristics of the resulting 142 patients that comprised our study population are described in detail in the Supporting Information. The median age at diagnosis was 44 years (range = 18–72). High-risk clinical features at diagnosis were observed as follows: 24% (n = 34) had a high WBC; 48% (n =68) had high-risk cytogenetics, with the majority of these (71%, n = 48) being Ph+; and 73% (n = 103) were over age

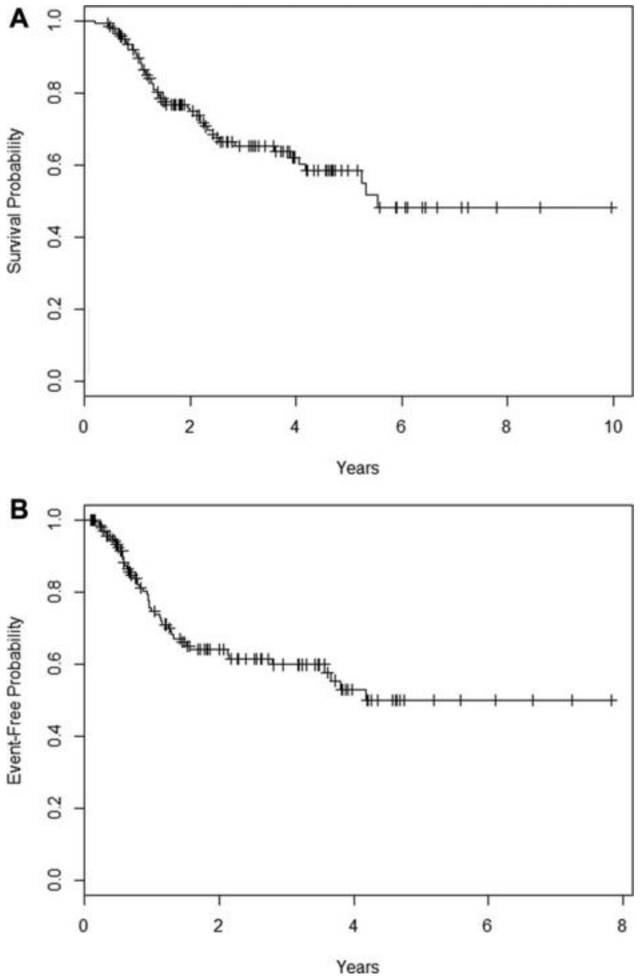

FIGURE 1 Kaplan-Meier curves depicting overall survival (A) and event-free survival (B) of patients who received hyperCVAD as front-line therapy for ALL. Time is measured in years from the start of the first cycle of treatment. Tick marks represent censoring at time of last known follow-up prior to an event or death

35. All Ph+ pts received TKI with hyperCVAD: 23 (48%) received imatinib and 25 (52%) received dasatinib. Rituximab was added to hyper-CVAD in 25 patients (18%), 8 of whom (32%) were also Ph+ and received concomitant TKI. In 5 patients (4%), asparaginase was incorporated to augment the regimen in a manner similar to that described previously.[25] Front-line HCT (ie, following remission achieved with hyperCVAD) was performed in 65 patients (46%), approximately 2/3 of which were performed using myeloablative conditioning. Kaplan-Meier curves depicting OS and EFS for the entire cohort are shown in Figure 1: 3-year OS was 65% and median OS was 5.6 years, while 3-year EFS was 60% and median EFS was 4.2 years. The median duration of follow-up for all surviving patients was 2.8 years (range: 0.4–9.9 years).

3.2 | Association between MRD and other factors

We then looked at the association between MRD and other factors likely to impact outcome in our cohort. Incidences of age over 35 years (72% vs 73%; $P = 1$), high-risk cytogenetics (46% vs 51%; $P = .72$), Ph+ (32% vs 38%; $P = .57$), and high WBC (21% vs 31%; $P = .21$) were lower, but not significantly so, among the patients that achieved MRD^{Neg} compared to MRD^{Pos} (respectively). Further, front-line HCT was utilized more often in MRD^{Neg} patients than in those who remained MRD^{Pos} during treatment with hyperCVAD (51% vs 33%, respectively), but not to a significant degree ($P = .07$). However, in Cox proportional hazards models adjusted for front-line HCT, cytogenetics, and WBC, MRD^{Neg} patients had significantly better OS (hazard ratio [HR] 0.43, 95% confidence interval [CI] 0.23-0.81; $P = .01$; 48 events) and EFS (HR 0.27, 95% CI 0.16-0.46; $P < .01$; 84 events) than MRD^{Pos}.

3.3 | Importance of time to MRD^{Neg} during HyperCVAD

Next, we aimed to determine the prognostic impact of the time needed to achieve MRD^{Neg}, acknowledging that the time of disease status assessment potentially varied case-to-case. The median time of first MRD assessment (relative to the start of treatment) was 37 days, with 27% occurring by 21 days and 85% by 90 days; 42% were MRD^{Neg} at this first assessment, 26% became MRD^{Neg} later, and 32% remained MRD^{Pos} despite a median of 2 (range: 1–5) assessments during the course of hyperCVAD. Of those with an MRD assessment within 21 days of starting hyperCVAD, 28% ($n = 11$) were MRD^{Neg}; among those with an assessment within 90 days, 50% ($n = 61$) had achieved MRD^{Neg}. In Table 1, a comparison of these results by Ph status, B vs T lineage, and laboratory where assessments were performed are shown.

Figure 2 depicts the cumulative incidence of achieving MRD^{Neg} over time. Among patients that became MRD^{Neg}, the median time to achieve this status was 68 days (range: 13–344 days). While achieving MRD^{Neg} still occurred later in treatment, the likelihood of achieving such a response wanes over time, with only 25% ($n = 24$) becoming MRD^{Neg} beyond 120 days and only 10% ($n = 10$) after 165 days. Roughly translating these time points into the treatment structure of hyperCVAD (assuming that each cycle spans approximately 21 days), 50% of patients who achieved MRD^{Neg} did so after 3 cycles (ie, cycle 2A), 75% were MRD^{Neg} after 6 cycles (ie, cycle 3B), and 90% after 8 cycles (ie, cycle 4B).

We also sought to understand the prognostic impact that time to MRD^{Neg} has in the context of hyperCVAD administration. As alluded to above, due to the varying times at which MRD was assessed in our cohort and the relative frequency at which patients achieved MRD^{Neg} over time, traditional proportional hazards models or landmark analyses would not be appropriate. Using a nonproportional hazards test and adjusting for front-line HCT (here included as a time-dependent covariate), cytogenetics, and WBC, time to MRD^{Neg} was highly significantly associated with EFS ($P = .009$), but not OS ($P = .19$).

The relationship between time to MRD^{Neg} and EFS is depicted in Figure 3 as a smoothed beta plot. This plot generally shows that as time to MRD^{Neg} increases along the x-axis, the log of HR [shown as "beta(t)"] for EFS generally increases via the spline smoothing. That being said, there are also several findings that deserve emphasis. First, the slope of the curve indicates that HRs are indeed nonproportional over time; if the HRs were proportional over time, the curve would be flat. Additionally, the generally positive slope suggests that a longer

TABLE 1 Frequency of achieving minimal residual disease negativity at specific times after starting hyperCVAD, based on Philadelphia chromosome status, lineage, and laboratory where assessments were performed

	B-ALL, Ph+			B-ALL, Ph−			T-ALL			P
Time & Lab	MRD^{Neg}	Assessed	%	MRD^{Neg}	Assessed	%	MRD^{Neg}	Assessed	%	
21 days										
UW	2	8	25%	4	7	57%	3	5	60%	
Other	1	6	17%	1	12	8%	0	1	0%	
Total	3	14	21%	5	19	26%	3	6	50%	.492
90 days										
UW	9	25	36%	17	27	63%	9	11	82%	
Other	6	18	33%	14	32	44%	6	8	75%	
Total	15	43	35%	31	59	53%	15	19	79%	.005
Ever										
UW	20	26	77%	20	30	67%	12	14	86%	
Other	11	22	50%	24	39	62%	10	11	91%	
Total	31	48	65%	44	69	64%	22	25	88%	.057

Abbreviations: B-/T-ALL, B-/T-lineage acute lymphoblastic leukemia (respectively); MRD^{Neg}, minimal residual disease negative; Ph, Philadelphia chromosome; UW, University of Washington Hematopathology Laboratory.
Time is relative to the start of hyperCVAD. *P*-values are from comparisons between Philadelphia chromosome status and lineage using Fisher's exact test.

time to achieve MRD^{Neg} is more hazardous [ie, higher value for beta(t) as time increases] than if it is achieved earlier [ie, lower value for beta (t) as time decreases]. The greatest increase in hazard is observed earlier, similar to a log function. Lastly, since the trend in the curve remains below 0, it implies that being MRD^{Neg} is always better than being MRD^{Pos} regardless of time, but again, it is less hazardous to achieve MRD^{Neg} sooner.

3.4 | Role of MRD assessment by RT-PCR in Ph+ ALL

Since RT-PCR was only used for MRD assessments in Ph+ patients, we investigated the impact of time to MRD^{Neg} when only results of MFC were considered. In our cohort, there were 7 patients with Ph+ ALL that had persistent MRD by RT-PCR but were MRD^{Neg} by MFC at a median time of 52 days (range: 18–113 days). After reclassifying these 7 patients as MRD^{Neg} based exclusively on the results of MFC and performing the same nonproportional hazards test (ie, adjusted for use of front-line HCT [again included as a time-dependent covariate], cytogenetics, and WBC), time to MRD^{Neg} was no longer associated with EFS to a statistically-significant degree ($P = .06$). Notably, of these 7 patients with Ph+ ALL who were MRD^{Neg} by MFC but persistently MRD^{Pos} by *BCR-ABL1* RT-PCR, 6 underwent HCT in CR1: 5 have neither relapsed nor died at a median follow-up of 21 months (range: 10–35 months)

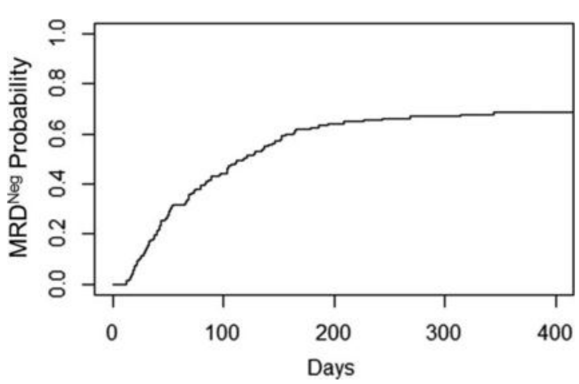

FIGURE 2 Cumulative incidence of minimal residual disease negativity (MRD^{Neg}) after initiation of hyperCVAD. Time is measured in days from the start of the first cycle of treatment

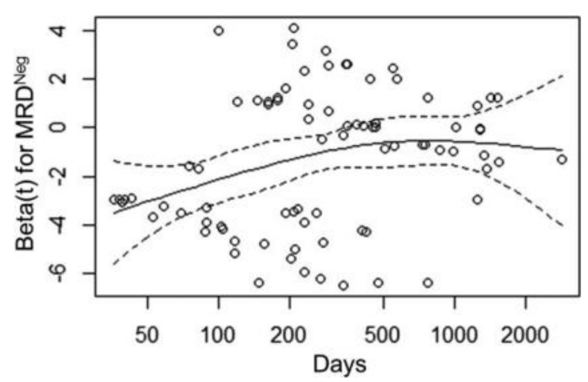

FIGURE 3 Smoothed beta plot showing the relationship between minimal residual disease negativity (MRD^{Neg}) and event-free survival (EFS) after treatment with hyperCVAD. Beta represents the log of the hazard of an event for patients that achieved MRD^{Neg}, with respect to the time at which MRD^{Neg} was observed. Time is measured in days from the start of the first cycle of treatment. Solid line is a line of best fit (via spline smoothing with 4 knots); dashed lines represent 95% confidence intervals. Open circles represent the contribution of individual patient events to this model

since starting hyperCVAD, while 1 patient (the one with the longest time to MRD^{Neg} [113 days]) relapsed after HCT and died 17 months after starting chemotherapy. The remaining patient from this subgroup died in remission 2 months after starting hyperCVAD.

4 | DISCUSSION

The incorporation of MRD monitoring into the treatment of ALL has become an accepted standard.[26] To date, however, its practical application into the commonly-used hyperCVAD regimen has been challenging due to the relative paucity of data available to guide such decision-making. Our analyses provide key new insights to help both practicing clinicians and clinical investigators better understand the role of MRD detection when using hyperCVAD, particularly as it relates to the general kinetics of response and the prognostic significance this holds.

One of the challenges in understanding the optimal timing of response assessment during hyperCVAD is its schedule of administration. Regimens with more canonical "Induction" and "Consolidation" courses lend themselves reasonably well to at least extrapolate results across studies with regard to risk stratification and/or treatment modification based on MRD. This does not apply as easily to hyperCVAD. This is reflected in the heterogeneous timing of MRD assessments within our cohort. Historically, our institution has not used a standard schedule of bone marrow examinations with this regimen. Alternatively, recent studies from MDACC have interpreted MRD status at relatively discrete time points: at the time of CR (ie, approximately day 21 of the first cycle) and at 3-month intervals thereafter.[15–17,27] This approach allowed for more uniform interpretation across patients and provided more power for these specific times. However, it also potentially missed the impact of other times in between. Our data, while heterogeneous in this regard, provide a more diverse assessment, particularly at more intermediate points 1–2 months into treatment.

A particularly compelling aspect of our analysis is the clear time-dependent nature of the prognostic impact of achieving MRD^{Neg} during hyperCVAD. Our data suggest that the earlier MRD^{Neg} is noted, the better the EFS will be. As a result, it is hard to define any specific inflection points at which prognosis clearly changes. If outcomes truly improve the earlier MRD^{Neg} is achieved, an assessment around day 21 (ie, after the 1st cycle) may identify a subset at the lowest risk of relapse. Considering that about half of patients in our cohort were alive and event-free beyond 3 years and 50% of patients who achieve MRD^{Neg} did so within 68 days (ie, roughly after the 3rd or 4th cycle), this may act as a reasonable threshold to start considering a patient at particularly high risk of relapse. Further, MRD persistence beyond 120 days (ie, after the 6th cycle) should raise serious concerns that MRD^{Neg} will not be achieved at all and a change in treatment is warranted. Again, our data are not able to clearly define such thresholds, nor are we able to comment on the appropriate strategies for patients with late clearance or overt persistence of MRD. These populations are clearly in need of continued investigation. It is also worth noting that this time-dependent relationship was not significantly linked to OS, though this may be ascribed to the relatively low number of survival events to include in the models ($n = 48$) or the ability to effectively salvage patients who relapse despite achieving MRD^{Neg}.[28]

The time-dependent nature of the prognostic impact MRD^{Neg} was weakened (albeit modestly) when we excluded the results of RT-PCR for *BCR-ABL1*. This raises several interesting questions about the relative importance of this method of MRD assessment, though the very small numbers of patients and events involved limit this to mere speculation. Despite having persistent MRD when considering either method, the 7 patients with discrepant results by MFC and RT-PCR did remarkably well: 1 death in CR1, and only 1 relapse among them in the patient with the longest time to MRD^{Neg} by MFC. Therefore, by reclassifying them as MRD^{Neg} for the purposes of our statistical modeling, one might have predicted the association between time to MRD^{Neg} and EFS would have been strengthened (ie, *P*-value would have dropped even lower). This however assumes that the results of *BCR-ABL1* RT-PCR are not important, which is not likely true.[16] Alternatively, it might be that the use of HCT in CR1 for 6 of these patients blunted the prognostic impact that a prolonged time to MRD^{Neg} would have otherwise had. We have previously shown that HCT in MRD^{Neg} CR1 can reduce the incidence of relapse but without a significant improvement in OS.[28] Again, while the numbers in this subgroup are far too small to draw definitive conclusions, it does perhaps suggest that the use of HCT for ALL in CR1 following hyperCVAD may be best utilized in those patients who achieve MRD^{Neg} but at a relatively late time point.

As only about one-quarter of patients in our study population had their first assessment within 21 days of starting treatment, our ability to comment on the relative importance of these very early times is limited. One of the above-cited studies by Short and colleagues from MDACC did evaluate the potential impact of MRD status as early as Day 14 of treatment.[27] They found that morphologic assessment at this time was significantly associated with subsequent MRD^{Neg}, EFS, and OS in multivariate analyses. However, when MRD status at the time of morphologic CR was included in their multivariate models, this early response assessment lost much of its prognostic significance. Since they also saw that virtually all patients ultimately enter a morphologic remission after starting this regimen, this makes MRD a particularly important part of understanding the likelihood of success with hyperCVAD.

Another noteworthy comparison between our study and other retrospective hyperCVAD-based analyses referenced is the relatively low rate of MRD^{Neg} in our cohort despite fairly similar survival outcomes across studies. In our cohort, 50% achieved MRD^{Neg} at 3 months, compared to approximately 90% at 3 months in the other hyperCVAD studies.[15,17] While we did consider results from *BCR-ABL1* RT-PCR as well as MFC performed at outside referring institutions, the most common method of MRD detection in this cohort was MFC performed at UW. This assay is used in prospective trials by the Children's Oncology Group and is about 1-log more sensitive than most other MFC platforms available (ie, 10^{-4} vs 10^{-3}, respectively). If a more sensitive assay is used to detect MRD, then fewer patients will be called MRD^{Neg}. This is particularly important as newer and more sensitive assays using high-throughput sequencing of *IGH* and *TCR* genes for

MRD in B- and T-ALL (respectively) are now available,[29,30] potentially making our data more applicable in the near future. Another potential contributor is that patients included in these other analyses were largely enrolled on prospective clinical trials,[17] whereas ours were not. This may then speak to an element of selection bias, though this would likely translate more into EFS and OS if it were truly a substantial difference between ours and other studies.

In addition to those already stated, this study does have several other important limitations. Due to the nonstandardized schedule, about 1 in 6 patients did not have their first MRD assessment until beyond 90 days. Since we cannot confirm MRD status until it is checked, this means that some patients in our cohort defined as MRD^{Neg} may in fact have been at this level for weeks. Had we been able to correct for this, it would have only strengthened our conclusions, as those who did well despite seemingly achieving MRD^{Neg} late in treatment would have been re-assigned into a group predicted to have done better. Also, nearly half of our cohort underwent HCT in first remission with the knowledge of their MRD status available to the treating physician, which may have impacted the outcomes. Given the limited data on the significance of MRD kinetics with hyperCVAD, it is unlikely that this would have been a major determinant for HCT referral. Moreover, we have previously shown that HCT in MRD^{Neg} first remission does not lead to a significant improvement in either OS or EFS after adjusting for other factors.[28] Lastly, as our study population is relatively small, we were limited in our ability to compare certain subgroups of interest. Patients with T-ALL may have achieved MRD^{Neg} more rapidly and frequently, but the strength of this conclusion is tempered by that fact that only 6 such patients were assessed within 21 days and only about one-fifth of the study population had T-ALL. Among those with B-ALL, patterns of response appeared similar between Ph- and Ph+, however.

In conclusion, not only is achievement of MRD^{Neg} a key prognostic marker in adults receiving hyperCVAD for initial treatment of ALL, but the time to achieve MRD^{Neg} is also an important consideration. Here, we have not only described in greater detail the general kinetics of response at the MRD level, but we have also shown that after adjusting for other factors known to impact outcome, earlier achievement of MRD^{Neg} leads to a significant improvement in EFS. These data provide important guidance for the optimal management of adults receiving this regimen, suggesting that patients who are relatively late in achieving MRD^{Neg} are less likely to do well and should be considered for alternative or investigational treatment strategies. Our results also provide insights to investigators seeking to improve upon historical results with front-line chemotherapy regimens for adults with ALL, particularly as MRD is poised to become an increasingly-utilized endpoint in clinical trials.[31]

CONFLICT OF INTEREST

Dr. Cassaday has received research support from Gilead, Incyte, Merck, Pfizer, and Seattle Genetics and has served on advisory boards for Amgen, Pfizer, and Adaptive Biotechnologies. Dr. Becker has received research support from Amgen, Glycomimetics, Bristol-Myers Squibb, JW Pharmaceuticals, and Abbvie and is on a Scientific Advisory Committee for Pfizer. Dr. Shustov has received research support from Pfizer. The remaining authors declare no potential conflicts of interest.

ORCID

Ryan D. Cassaday http://orcid.org/0000-0002-3424-2425
Brenda M. Sandmaier http://orcid.org/0000-0002-9767-9739

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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