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Need for consensus on primary end points and efficacy definitions in trials for adult acute lymphoblastic leukemia

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The lack of consensus on acceptable primary end points and definitions of response and survival in phase 2/3 efficacy studies for adult acute lymphoblastic leukemia has led to widely different clinical trial designs. Inconsistency in primary end point selection and lack of consensus on response, survival end points, and adequate follow-up time lead to difficulty in interpreting completed studies and developing future trials. The lack of consensus also runs the risk of integrating ineffective or unacceptably toxic regimens into clinical practice and future trials. Increasingly, studies integrating highly active, targeted agents into chemotherapy use short-term end points of response, measurable residual disease–negative response, and early event-free survival without confidence that these end points will translate into improved late patient outcomes. This article highlights the current consequences and dilemmas caused by this lack of consensus. The hope is to stimulate discussion and ultimately consensus to improve the interpretation and application of clinical trial results.

Introduction

Acute lymphoblastic leukemia (ALL) is a rare malignancy characterized by the uncontrolled proliferation of B-cell or T-cell precursors. Until the success of the targeted BCR::ABL1 tyrosine kinase inhibitor (TKI) imatinib for Ph^+ ALL,[1] conventional cytotoxic chemotherapy treatment alone lasting 2.5 to 3.5 years and allogeneic hematopoietic cell transplantation (HCT) were the available treatments. Relapse after initial therapy was associated with a survival rate of 7% in the absence of allogeneic HCT.[2] The anti-CD22 antibody-drug conjugate inotuzumab ozogamicin and anti-CD19 bifunctional T-cell engager blinatumomab have been Food and Drug Administration-approved for the treatment of relapsed B-cell ALL based on phase 3 studies showing superior overall survival (OS) compared with conventional salvage chemotherapy.[3,4] Notably, both drugs led to high measurable residual disease (MRD) negativity rates at complete remission (CR; inotuzumab ozogamicin 78%; blinatumomab 76%), yet remissions were not durable (inotuzumab ozogamicin, median duration of remission 4.6 months; blinatumomab, median duration of remission 7.3 months). The high activity of inotuzumab ozogamicin and blinatumomab in the relapsed ALL setting has led to clinical trials integrating the agents into frontline therapy for newly diagnosed B-cell ALL.

Because of the rarity of ALL and the lack of wide national/international collaboration, the treatment of adult ALL has been predominantly based on single-arm clinical trials and nonrandomized, retrospective comparisons of treatment approaches. With improved collaboration, recent phase 3 studies have shown improved event-free survival and OS with the addition of targeted therapies to frontline chemotherapy.[5,6] With the advent of highly active, targeted agents applied early in ALL treatment, achieving deep MRD-negative CR early in therapy has become achievable for most patients with ALL.

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However, unlike with conventional chemotherapy, it is unclear whether these early MRD-negative states consistently translate into improved long-term survival outcomes. Late relapse and toxicity with targeted agents may eliminate long-term benefits, even with excellent early outcomes. The risk of using short-term primary end points is integration into treatment guidelines and clinical practice of regimens that may lack adequate long-term safety and efficacy data. In addition, a lack of consistency in the definitions of events for survival end points and minimum meaningful follow-up can make study interpretation difficult and may hinder the optimal understanding and development of clinical trials.

Response as a primary end point: a reliable survival surrogate with targeted therapies?

Until the recent integration of targeted agents into frontline therapy, the treatment of newly diagnosed ALL typically included intensive, multiagent chemotherapy with anthracycline, vincristine, and corticosteroid-based remission induction followed by allogeneic HCT or intensive postremission chemotherapy and 2 to 3 years of low-intensity maintenance chemotherapy. MRD negativity at CR early in intensive, conventional chemotherapy predicts high leukemia-free survival and OS rates with conventional postremission chemotherapy in pediatric and adult populations.[7-10] MRD positivity at CR predicts the benefit of myeloablative allogeneic HCT compared with chemotherapy.[11-13] Thus, MRD is useful in risk stratification and allocation to allogeneic HCT. Outside of intensive, conventional chemotherapy regimens, such as those integrating targeting agents or conventional chemotherapy-free regimens, the utility of MRD-negative CR in predicting long-term cure rates and OS is not well known. With the application of highly active, targeted therapies (eg, BCR::ABL1-targeted TKIs and inotuzumab ozogamicin) for newly diagnosed Ph^+ and Ph^- B-cell ALL, achieving CR to induction is possible for 90% to 100% of patients with MRD-negativity rates of 70% to 90% but this has not consistently yielded proportionally improved disease-free survival (DFS) or OS compared with conventional chemotherapy.[14-17] Despite this, MRD-negative CR is increasingly being used as a surrogate marker in studies using novel targeted therapies, for which the value of this end point has not been well defined. MRD negativity, however, does not appear to routinely equate with the high OS and relapse-free survival (RFS) seen with early MRD negativity with conventional chemotherapy in younger adults.

Several recent trials integrating targeted therapies into frontline therapy for ALL, none using MRD as part of the primary end point, have highlighted the potential risks of including MRD as part of a primary end point. The US cooperative group study Southwest Oncology Group 1318 studied the CD19-CD3 bifunctional T cell engaging antibody blinatumomab for induction and consolidation followed by mercaptopurine, vincristine, methotrexate, and prednisone maintenance in older adults with newly diagnosed Ph^- B-cell ALL. The CR rate was 66% but with a 92% MRD-negativity rate at CR. Despite the high MRD-negativity rate at CR, the median DFS was 1.3 years, and the 3-year DFS 37% without a clear plateau in events.[14] Three recent studies have reported the outcomes of integrating the anti-CD22/calicheamicin antibody-drug conjugate inotuzumab ozogamicin into frontline therapy for older patients with Ph^-, $CD22^+$, and B-cell ALL. The GMALL INITIAL-1 trial of inotuzumab ozogamicin alone as induction followed by conventional chemotherapy reported a CR rate of 100% with an MRD-negativity (10^{-4}) rate of 72%. With 2.7 years median follow-up, OS was excellent (estimated 73% at 3 years), with an estimated event-free survival (EFS) of 55% at 3 years.[15] The EWALL-INO regimen used inotuzumab ozogamicin with low-intensity chemotherapy as induction, followed by conventional chemotherapy. The induction CR rate was 90% with an MRD-negativity ($<10^{-4}$) rate of 81%. The leukemia-free survival and OS at 2-years were 50% and 54%, respectively.[16] MD Anderson studied inotuzumab ozogamicin in combination with reduced-intensity chemotherapy (hyperfractionated cyclophosphamide, vincristine, and dexamethasone alternating with methotrexate and cytarabine [miniHyperCVD]) with or without blinatumomab. The CR rate was 99% (91% after 1 cycle), with an MRD-negativity rate of 94%. Five-year progression-free survival and OS rates were 44% and 46%, respectively.[17] The above studies are all nonrandomized but demonstrate that MRD negativity with targeted therapies, although a positive goal of treatment, does not necessarily translate into excellent long-term outcomes as seen with intensive chemotherapy in younger adults and pediatric patients due to high rates of late relapse or nonrelapse mortality.

In Ph^+ ALL, improved early response with BCR::ABL1-targeted TKIs has not always translated into improved long-term EFS or OS. An early study of imatinib showed that adding imatinib with conventional chemotherapy (HyperCVAD) was more toxic than imatinib with reduced-intensity chemotherapy. Imatinib + reduced-intensity had a higher CR rate (98% vs 91%; $P = .006$) due to a higher early death rate with imatinib-HyperCVAD (0.7% vs 6.7%; $P = .01$). No difference, however, was seen in 5-year EFS or OS.[18] The Takeda-led PhALLCON study randomized patients to ponatinib or imatinib with reduced-intensity chemotherapy. The primary end point with MRD-negative CR for 4 weeks after the end of induction. The MRD-negative CR rate was superior with ponatinib (34% vs 17%; $P = .002$).[19] But this end point is not validated nor representative of the biology of resistance to BCR::ABL1-targeted TKIs, which is largely through ABL1 kinase domain mutation, and not early primary resistance.[20-22] The difference in this end point is likely due to differences in drug potency, as ponatinib is significantly more potent than imatinib.[23] To date, there has been no significant difference in EFS or OS reported.

Despite these outcomes and lack of validation of the end point as a surrogate for survival, numerous randomized trials are now using MRD-negative CR as, or as part of, a primary end point (Table 1). Approving or recommending a treatment or treatment approach based on an early response end point is potentially dangerous, as early end points can be easily manipulated in clinical trial design to achieve a predesired result that may not correlate with long-term disease control or OS. In addition, using early, unvalidated surrogate end points as primary end points runs the risk of adopting or approving therapies that may have substantial late toxicities not represented in the early response primary end point. Such studies may be erroneously declared "successes" by satisfying a primary end point that does not capture relapse rates and toxic death rates, thereby failing to serve trial subjects and patients.

EFS: a powerful end point with inconsistent definitions

Definitions of EFS (and DFS/RFS) vary by study. EFS typically includes refractory disease, progressive disease, relapse, and

Table 1. Primary end points in ongoing randomized adult ALL trials

NCT identifier	Treatments	ALL status	Age, y	Primary end point
Phase 2				
NCT05748171	Inotuzumab ozogamcin vs ALLR3 chemotherapy	First relapse	1-18	MRD negativity in participants achieving CR, complete response with incomplete platelet count recovery (CRp), or complete response with incomplete count recovery (CRi)
NCT05082519	Caloric restriction (to reduce chemotherapy resistance) vs none	Untreated	10-25	End induction MRD positivity
NCT04920968 (PALG ALL7)	Obinatuzumab + chemotherapy vs rituximab + chemotherapy	Untreated	18+	End induction MRD-negative CR rate
NCT05303792 (A042001)	Inotuzumab ozogamicin + lower dose chemotherapy vs age-adjusted chemotherapy	Untreated	50+	EFS including failure to achieve MRD-negative CR, 2-mo
Phase 3				
NCT04307576 (ALLTogether)	Multiple agents/randomizations	Untreated	0-45	EFS, 5-y
NCT02881086 (GMALL08)	CNS irradiation in combination with intrathecal therapy vs intrathecal therapy and allogeneic HCT vs chemotherapy	Untreated	18-55	EFS, 3.5-y
NCT03821610 (ALL-RIC)	Total body irradiation/cyclophosphamide vs fludarabine/melphalan conditioning	Untreated	40-70	DFS, 2 y, transplant study
NCT03959085 (AALL1732)	Inotuzumab ozogamicin + mBFM(-DI2) vs mBFM	Untreated	1-25	DFS, 5-y from end of consolidation
NCT02611492 (GRAAPH2014)	Nilotinib + SD chemotherapy/HCT vs nilotinib + RI chemotherapy/HCT	Untreated	18-59	Major molecular response at 4 mo
NCT04722848 (ALL2820)	Ponatinib + blinatumomab vs imatinib + chemotherapy	Untreated	18+	EFS, 5 mo
NCT04530565 (EA9181)	Steroids + TKI + blinatumomab induction vs steroids + TKI + chemotherapy induction	Untreated	18-75	OS
NCT03150693 (A041501)	Inotuzumab ozogamicin + chemotherapy vs chemotherapy	Untreated	18-39	EFS, 3-y
NCT04994717 (Golden Gate)	Blinatumumab + low-intensity chemotherapy vs standard chemotherapy	Untreated	40-100	EFS, including failure to achieve MRD-negative CR, 5-y; and OS, 5-y

CNS, central nervous system; mBFM, modified Berlin-Frankfurt-Munich; NCT, National Clinical Trial; RI, reduced intensity; SD, standard dose.

death from any cause as treatment failure events. A number of other events have been included in studies, including failure to achieve MRD negativity at a defined time point, MRD recurrence, initiation of alternate therapy, failure to complete therapy, and the development of secondary malignancy. Inconsistent definitions of EFS make the interpretation of single-arm clinical trial results difficult across studies, thus hindering the successful development of future randomized and nonrandomized studies. In addition, not all events were equal. Some events for EFS may be clinically meaningless, not directly related to the regimen itself, or can be modified to suit the desired study outcome. Among the clinically meaningful events, death related to the study therapy was clearly worse than relapse. A consensus on these study outcomes is needed to provide more clarity regarding the meaning of study outcomes across single-arm and randomized studies in ALL.

The time set for event analysis also varied widely among active randomized studies, from 2 months to 5 years in currently active studies (Table 1). In 4 randomized, phase 2 studies, all used early response end points as the primary end point and 3 in untreated patients. This is not trivial, as the addition of targeted agents to conventional chemotherapy regimens may, as above, cause significant toxicity and negatively impact late outcomes, while improving early outcomes, such as CR and MRD negativity.

Late toxicity may be so substantial as to consider some regimens unacceptably toxic. When combined with chemotherapy, inotuzumab ozogamicin, despite very high rates of MRD-negative CR in induction, may not improve EFS or OS due to late toxicity and death in remission. The EWALL-INO study had a 16% death in remission rate with 15 months of follow-up[16] and the GMALL INITIAL-1 study had 17% at 3 years.[15] Similarly, the addition of inotuzumab ozogamicin to miniHyperCVD was designed as a regimen to reduce toxicity and improve efficacy for older patients with ALL but had a high 44% death in remission rate in the last report.[12] Despite the extraordinarily high rate of death in remission, in a single-center study of a highly selected patient population, the regimen continues to be studied in an ongoing trial using a 2-month EFS primary end point (NCT05303792) and is currently part of the National Comprehensive Cancer Network Guidelines recommendations.

Based on the above, early EFS end points should be considered unacceptable in most phase 2 and 3 ALL trials integrating novel therapies unless they have been demonstrably validated in

prospective studies of the drugs being studied. Using early EFS end points may place trial subjects, and ultimately patients, at substantial risk. Harmonizing expectations as to the appropriate follow-up time for reporting EFS and OS would allow better evaluation of both the safety and efficacy of regimens in phase 2 and 3 studies. The follow-up time may vary to some degree by study type and population but should be adequate to capture the most meaningful late events.

Should the gold standard of OS change?

The rarity of ALL and the need to study subgroups with newer targeted agents creates a serious issue powering studies for OS. With national and international multicenter collaboration, it has been possible even in population subsets, as evidenced by the success of the recently reported ECOG-ACRIN study E1910, a randomized phase 3 study that met its primary end point by showing a significant OS benefit with the addition of blinatumomab to postremission chemotherapy for adults with B-cell ALL.[6] EFS is a commonly used primary end point in phase 2 studies but is increasingly being used in randomized phase 3 studies as well (Table 1). OS in adult ALL historically parallels EFS closely although this may be changing with better salvage therapies. In addition, as EFS is currently poorly defined between studies, OS with adequate follow-up time remains the gold standard as a primary end point, even if it is difficult to power for in some ALL studies. With better consensus on the definitions of EFS and meaningful follow-up time, it may become an excellent surrogate for OS and useful for small populations, such as extremes of age or genetic subsets, although this would need to be established prospectively.

Conclusion

At this time, early MRD response end points, either alone or as part of the EFS, appear to be inappropriate for randomized studies using highly active targeted therapies in ALL. If EFS can be consistently defined across ALL trials, powering all studies to OS should be unnecessary during the early exploration of novel regimens. National and international consensus on response and survival definitions would be needed to move toward this improvement in ALL clinical trial design.

Questions for national/international consensus for phase 2 and 3 ALL trials include:

- When is response, including MRD response an acceptable primary end point?
- How should remission, MRD negativity, and relapse be defined?
- How should EFS (and DFS/RFS) be defined?
- When is OS an essential end point?
- What is an adequate duration of follow-up for response and survival end points?
- What rate of death in remission is considered excessive?

With consensus, clinical trial design can be harmonized to more consistently derive interpretable results from ALL trials. In addition, consensus will help agencies, editors, and reviewers of abstracts and manuscripts assess proposed, ongoing, and completed studies for scientific rigor and appropriateness for funding, presentation, and publication. As patient survival improves and targeted approaches expand, more collaboration within and among nations conducting trials in ALL will be needed to power studies and make definitive progress. Establishing an early consensus on the study end points will facilitate consistent clinical trial design and conduct. In addition, as OS improves, it becomes even more important, even if more logistically difficult, to use survival with reasonable follow-up as a primary end point, as the addition of novel agents runs the risk of worsening outcomes if studies have an inadequate follow-up.

Authorship

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