Allogeneic Marrow Transplantation in Children with Acute Leukemia: Careful Comparison to Chemotherapy Alternatives Required

Don Pinkel has a tremendous record of accomplishment in the development of modern therapies for childhood acute lymphoblastic leukemia (ALL). He played a pivotal role in the development and evolution of early "Total Therapy" studies for childhood acute lymphoblastic leukemia (ALL) at St. Jude Children's Research Hospital in the 1960s and 1970s. He dared to believe that this, until then, universally fatal disease could be cured and saw his dreams come true. At about the same time, others, most notably Don Thomas, dared to believe that allogeneic hematopoietic stem cell transplantation (HSCT) could cure patients with leukemia. Time has shown that both Don Pinkel and Don Thomas were correct. Today, over 80% of children diagnosed with ALL in North America and Western Europe will be cured and HSCT has cured thousands of children and adults with leukemia, bone marrow failure states, and other disorders.

Given this background, we are troubled by Dr. Pinkel's recent editorial updating his view that the use of allogeneic HSCT to treat children with leukemia is "a practice whose time has gone" (Leukemia (2009) 23, 2189–2196). While we wish that all children with leukemia could be cured with chemotherapy and therefore have no need for HSCT, this is simply not the case today, and is unlikely to become true in the near future. As specialists in the treatment of childhood leukemia, with or without HSCT, we believe our job is to carefully weigh the relative advantages and disadvantages of chemotherapy or HSCT approaches in different clinical settings, develop rational treatment algorithms, and design clinical trials to answer critical questions. We believe that Dr. Pinkel's editorial fails to put these different treatment modalities in the proper perspective and are particularly concerned that his portrayal of HSCT as curing children

at the cost of universal, significant late-effects, while late-effects of chemotherapy approaches are not mentioned, paints an inaccurate picture. Similarly, we are concerned that studies showing advantages in survival with HSCT in certain disease states were brushed aside by speculation of bias.

Stem cell transplantation is in some ways an easy target. It is a complicated treatment modality that is advancing and changing rapidly, requiring focused attention to maintain a contemporary knowledge base from which medical advice can appropriately be made. Reliance upon out-dated studies risks invalid assumptions. A simple fact must be remembered in this discussion: the approach works. It is a well-established, ethical, non-experimental therapy for children that cures leukemia. Major progress has been made over the past two decades in HLA typing, stem cell source choices, GVHD prevention, transplant-related mortality, and cure rates after unrelated donor transplantation.(1) The large majority of children who undergo HSCT live happy, productive lives, with good health, and normal growth and development.

A better approach is an ongoing, rigorous assessment of the changing field leukemia therapy, making judicious, and as much as possible, data-driven choices of when to give more or less intense therapy. This includes a careful judgment of when risk of relapse is high enough to justify the use of allogeneic HSCT, and for what disease states there is solid empirical evidence that HSCT provides a survival advantage in comparison to other treatment approaches. We agree with several points that Dr. Pinkel made: reasonable comparative studies have shown that most infants with ALL do not benefit from HSCT in CR1, evidence is emerging that most patients with Ph+ ALL may also no longer require CR1 HSCT (assuming long-term data from the COG AALL0031 trial(2) continue to show prolonged DFS), and children with better-risk AML do not require HSCT from matched siblings in CR1. However, there are children who benefit from transplant (Table 1). A more detailed review of our recommendations regarding the

role of transplantation for children with ALL and AML is in preparation, but several points made in Dr. Pinkel's editorial need to be addressed quickly. In addition, we will outline a few principles that should be considered when evaluating studies that attempt to compare chemotherapy and HSCT outcomes.

We struggle with Dr. Pinkel's claim that use of allogeneic HSCT is not justified because it deprives children of the goal of all cancer therapy: "normal health with normal capacity for growth and development." He lists offenses of HSCT including chronic graft versus host disease (GVHD), multiple endocrine disorders, second cancers, sterility, renal insufficiency, obstructive and restrictive pulmonary disease, aseptic necrosis of bone and leukoencephalopathy. Yes, some children treated with HSCT die of treatment complications and others have major long-term side effects. Unfortunately, the same is true for chemotherapy treatments, particularly those used for treatment of high-risk subsets such as infants with ALL, or children and adolescents with relapsed/refractory ALL and AML. Many of the adverse effects associated with both treatment modalities occur because of prior therapy. Studies that simply catalogue late effects after HSCT do not help address comparison of approaches. The best studies put HSCT therapy in the context of the many treatments patients with high risk leukemia receive and attempt to define specific therapies that are associated with late effects. A recent example is found in a study by Goldsby et al which showed that late neurological effects in ALL patients were associated with several factors including relapse, but not with HSCT.(3) Patients and parents will make better choices when informed what late effects risk they already have, and what increase in risk they have after HSCT versus what increase they will have if chemotherapy is chosen.

A second issue of concern to Dr. Pinkel is possible bias in studies that compare outcomes of chemotherapy or HSCT for various subsets of childhood leukemia. We all struggle with the fact that well-designed randomized controlled trials of HSCT versus

chemotherapy have not been conducted successfully. However, this does not mean that nothing can be concluded from the comparative studies that have been conducted. Dr. Pinkel states that in such studies “many risks for treatment failure are unaccounted for such as socio-economic and insurance status, ethnicity, geographic residence and venue of patient care. Children receiving allo- HCT are usually treated in larger well-staffed centers with more abundant resources.” We agree that many of these issues could cloud the assessment of comparative studies of chemotherapy vs. transplant. We are not familiar with evidence supporting Dr. Pinkel’s assertion that smaller centers disproportionately use chemotherapy compared to larger centers, as the use of HSCT is generally based upon the assumptions and experience of the treating physician, and many larger centers prefer chemotherapy approaches, while many smaller centers refer patients to other sites for HSCT, particularly after relapse has occurred. We welcome study of this question, along with the other factors mentioned. Improvements in cord blood transplantation over the last several years has largely addressed issues of access to unrelated HSCT, allowing Black, Hispanic, and Asian/Pacific populations formerly unable to find adequate HLA matches the ability to undergo safer, more efficacious procedures (>90% of children from all ethnic backgrounds now have acceptable cord blood matches in the registry if other stem cell sources are not available). Survival outcomes of recipients of appropriately matched and dosed cords are now equivalent to recipients of matched unrelated donors.(4)

Along similar lines, one would also need to consider legitimate concerns that a decision to refer a patient for HSCT may reflect the physician’s assessment of the patient as being higher risk, compared to those receiving chemotherapy. Clinicians may prefer chemotherapy treatment in patients who respond rapidly, while those same clinicians may refer their more worrisome patients for HSCT (i.e. those with poor response or a history of complications with or inability to tolerate important

chemotherapy agents such as vincristine, asparaginase , etc.). As opposed to Dr. Pinkel's assertion that non-measured biases are working in favor of better outcomes for HSCT, it is possible that biases in comparative trials may favor chemotherapy. With this in mind, trials should be designed to gather sufficient information to minimize bias. To illustrate this point, we will review two trials discussed by Dr. Pinkel that illustrate the pitfalls of comparative studies, and then contrast them with two comparative trials that incorporate design elements that greatly improve the validity of their conclusions.

The first trial to mention is the UKALLR1 study.(5) The study design intended treatment of higher risk patients with matched sibling allogeneic HSCT, while those not having an available sibling donor were to be randomized between autologous HSCT and chemotherapy. Though the design seemed reasonable, emerging data during the trial period showed no advantage of autologous transplantation over chemotherapy, and success with unrelated donor HSCT led some clinicians to pull their highest risk patients off the trial for this therapy. This led to an astonishing outcome: *only 9% of eligible patients were randomized as intended.* By modern standards this trial would have closed and comparative analysis deemed impossible. Instead, a comparison of related donor HSCT vs. unrelated donor HSCT vs. autologous HSCT vs. chemotherapy was attempted, in spite of the admission by the authors that the groups were not comparable by risk factor profile. A "statistical correction" for risk was included, but when the choice of unrelated HSCT is heavily weighted toward increased risk, and other therapies are applied by clinician preference, post-hoc statistical correction of biased assignment to consolidation therapies is impossible. The lesson from the UKALLR1 trial is that a fair comparison of chemotherapy with HSCT must be either planned and carried out properly, or based upon risk. Mixing groups of different risk may cancel an effect, because high risk patients, who may benefit more from HSCT, can be diluted by

intermediate risk patients, where transplant outcomes could either be similar to chemotherapy or worse.

A second comparison, put forward by Dr. Pinkel as evidence that HSCT outcomes are not different compared to chemotherapy for relapsed ALL, instead shows that conclusions cannot be drawn when critical data are not available. The paper described survival outcomes of patients of patients treated initially on the CCG-1952 standard risk ALL study who relapsed.(6) While the global picture of how patients do after relapse was valuable, an opportunity to compare HSCT with chemotherapy was lost because critical details about the HSCT procedures were not available, and risk-based analysis was not performed. Of the 89 patients undergoing HSCT, the stem cell source was unknown in 39 (44%). Among the cord blood, unrelated donor and sibling stem cell sources that were known, degree of HLA match was not available. The type of preparative regimen and whether the patient was in remission at the time of transplant was unknown. There are major differences in outcome in ALL patients with TBI vs. non-TBI regimens, partially mismatched vs. matched related and unrelated HSCT, and most importantly, patients who go to transplant in CR vs. active disease. The authors of this paper excluded from analysis those in the chemotherapy cohort who had a second relapse or who died prior to day 130 (median time to transplant), but did not exclude those in the transplant group who had a second relapse and still went to transplant or who went to transplant with active disease. The global picture of what happens to patients after relapse presented in this publication is useful, but the analysis of HSCT vs. chemotherapy outcomes is not helpful and does not inform treatment decisions. Furthermore, outcomes of primary therapy for standard risk ALL patients have improved significantly over those attained in this study, so the population of standard risk ALL patients that relapse now is likely quite different than the CCG 1952 relapse population. Thus, a patient with standard risk ALL that relapses today and has a matched donor who

is eligible for a TBI-based procedure gains no insight into whether they should choose chemotherapy over HSCT based upon this paper.

Two other studies illustrate approaches that allow more informative comparison of HSCT with chemotherapy. Eapen et al compared well-established risk groups, early (<36m from diagnosis) and late (≥36m from diagnosis) BM relapse with transplantation from matched siblings vs. chemotherapy given on high-quality, era-appropriate chemotherapy from three POG relapse trials.(7) All patients achieved a second remission, median time to transplant was corrected for, and transplant regimens were known. A significant difference in DFS was noted with TBI-based transplant vs. chemotherapy approaches in early relapse, while outcomes were equivalent for late relapse. Dr. Pinkel mentions this paper briefly, but dismisses it because of a lack of overall survival data. Overall survival data *was* included in this publication, and it was also highly statistically significant (see Table 2). This study illustrates the necessity of only including patients who achieve remission, knowing the details of the transplant therapy they receive, and comparing similar risk groups. A second example of a different, valid comparative study design is found in a report analyzing the outcomes of high-risk T-ALL in the BFM 90 and 95 trials.(8) The investigators appropriately did the following: 1) defined a high risk population with poor chemotherapy outcomes with current era approaches, 2) included only patients who achieved remission and timed outcomes from the time remission was achieved, 3) assigned an “SCT” cohort based upon the presence of a matched sibling donor and transplanted them with an effective regimen, 4) corrected the chemotherapy cohort for median time to transplant, and 5) performed an intent-to-treat analysis. The study showed a statistically significant improvement in DFS by intent-to-treat (Table 2), with a more significant difference noted according to actual therapy received. Much about the outcomes of this study has changed. Better results are now obtained with chemotherapy for children with high-risk

T-ALL, and HSCT indications have changed. However, the principles behind this study design and analysis are sound.

In summary, it is vital that investigators continuously evaluate the role of allogeneic HSCT in the treatment of children with leukemia as chemotherapy and HSCT treatment modalities evolve. Studies must include data necessary to assess HSCT appropriately: state of remission at transplant (MRD status if possible), stem cell source (with HLA matching and cell dose), preparative regimen, and whether therapy to treat relapse after transplant was successful. Studies should compare risk groups that are similar, as HSCT may have different risk/benefit ratios with different risk groups, and lumping of groups of different risk in order to obtain statistical power may inadvertently hide an advantage in one of the risk groups. Analyses of specific transplant interventions should either start at the attainment of initial remission, or only include patients who achieve remission and maintain that remission to time of transplant. Inclusion of patients who fail to achieve remission (for whom both chemotherapy and HSCT are futile therapies) may prejudice outcomes against a smaller or an unbalanced cohort. Finally, studies of late effects of HSCT should attempt to discern what HSCT adds to the late effects risk patients already have with the sometimes extensive, intense chemotherapy treatment they have received prior to transplant, and contrast that with additional risks added by chemotherapy approaches. All of this information can help families put survival statistics of HSCT or chemotherapy in context and aid them in making the best decision for their therapy.

Respectfully,

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Table 1. Current COG Indications for Allogeneic HSCT in Pediatric ALL and AML

ALL	AML
CR1 • Primary induction failure • t(9:22) Philadelphia chromosome–positive[1] • Extreme hypodiploidy (<44 chromosomes)[2]	CR1 High risk • Monosomy 5 or 7, 5q- • Induction failure (> 15% bone marrow blasts after one induction cycle of chemotherapy or ≥ 5% bone marrow blasts after two induction cycles of chemotherapy) • high FLT3-ITD AR >0.4 Intermediate risk[3] • All patients who are not high risk or low risk (low risk = favorable cytogenetics *(inv(16)/t(16;16)*, *t(8;21)*))
CR2 High risk • B-cell: BM relapse < 36m from diagnosis • T-cell or Ph+: BM relapse at any time Intermediate risk[3] • Isolated extramedullary relapse within 18 months of diagnosis • B-cell: BM relapse ≥ 36m from diagnosis	CR2 • All patients, especially if leukemia relapse within 12 months
CR3+ • Any second or greater relapse, whether marrow, isolated extramedullary relapse, or combined	CR3+ • All patients

[1]Early data from a COG study shows promising 3-year survival with chemotherapy.(2) HSCT indicated on current trial if matched sibling present or persistent MRD noted.
[2]Indication on COG trials, limited comparative data available
[3]Intermediate risk patients are only offered matched sibling donor HSCT.

Table 2. Survival Outcomes of Two Studies where More Informative Comparative Methodology was Employed

Study	Risk Group	Chemotherapy Outcomes	HSCT Outcomes (% with 95% CI)	p-value
Eapen *et al(7)*	HR CR2 (rel <36m from dx)	EFS 23% (15-31) OS 32% (23-40)	EFS 41% (31-52) OS 44% (33-55)	0.003
	Intermed Risk CR2 (rel≥36m)	EFS 59% (47-69) OS 66% (54-76)	EFS 60% (46-71) OS 63% (49-74)	0.49
Shrauder *et al(8)*	HR T-cell ALL	EFS 45±7%*	EFS 72±11%	0.045

*This intent-to-treat analysis is of the BFM 95 cohort. Patients who went off study for alternative HSCT were censored at the time of HSCT.

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