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Is Allogeneic Stem Cell Transplantation of High-Risk Pediatric Acute Lymphoblastic Leukemia (ALL) Patients More Effective In Preventing Future Relapses of Disease and/ or Mortality In Comparison With Chemotherapeutic Regimens Alone?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences - Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
Philadelphia, Pennsylvania

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ABSTRACT

OBJECTIVE:

The objective of this selective EBM review is to determine whether or not allogeneic SCT of HR pediatric ALL patients is more effective in preventing future relapses of disease and/or mortality in comparison with chemotherapeutic regimens alone.

STUDY DESIGN:

Review of three English language primary randomized controlled trial studies published between 1996 and the present.

DATA SOURCES:

Randomized controlled trial studies were found using PubMed.

OUTCOMES MEASURED:

Each of the three studies evaluated the incidence of recurrent disease and/or mortality in high-risk pediatric ALL patients. These outcomes were analyzed according to the following categories: duration of event-free survival (EFS); duration of disease-free survival (DFS); incidence of relapses; complete remission (CR); death; partial response (PR); resistant disease (RD); and overall survival (OS).

RESULTS:

Three randomized controlled trials were included in this review. The study by Schrauder et. al., which analyzed the role of SCT in first complete remission for children with very high-risk ALL, showed that the OS for patients who received SCT was higher than that of the patients who received chemotherapy alone (67% vs. 47%). In the study by Ribera et. al. comparing the options of chemotherapy alone versus allogeneic SCT as post-remission therapy, the DFS and OS were both used as indicators of success and showed higher percentages of both in the subgroup that received chemotherapy alone. The final study by Tallen et. al. analyzed a multicenter trial (ALL-REZ BFM 90), which was created with the purpose of improving the prognosis for children with relapsed ALL. The results of this study demonstrated significant differences in the probabilities of EFS and OS amongst the different subgroups analyzed indicating that remission induction regimens must be improved and that allogeneic SCT should be recommended in patients achieving a second complete remission.

CONCLUSIONS:

Two out of three studies included in this review support the use of allogeneic SCT versus chemotherapeutic regimens alone when treating high-risk pediatric ALL patients. Various factors, such as the achievement of first versus second remission, can also affect the results of studies involving this patient population.

KEY WORDS:

Allogeneic stem cell transplantation, acute lymphoblastic leukemia, pediatric

INTRODUCTION

Pediatric acute lymphoblastic leukemia (ALL) is a malignant disease of the blood and bone marrow, that initiates with the lymphocytes (or lymphoblasts, an immature lymphocyte), a specific type of white blood cell (WBC) in the bone marrow, that are crucial in immune system functioning. Once ALL develops, it then invades the bloodstream and can infest various organs, such as the liver, spleen, and lymph nodes.¹ Pediatric ALL has a rapid onset of symptoms that can be fatal if not immediately treated. Symptoms of pediatric ALL are often vague and can mimic many other medical conditions making it difficult to diagnose at times; therefore, it is important for practicing physician assistants (PA) to be more aware of this deadly disease since it can cross over into many scopes of PA practice (i.e. family medicine, general pediatrics) and should be recognized so that prompt treatment can be initiated.

Although it is recognized as one of the more “curable” types of childhood cancer, approximately 30% of patients relapse.² Various prognostic factors of pediatric ALL patients include age and WBC count at the time of diagnosis, type of lymphocyte involved, specific chromosomal translocations, and patient’s response to induction chemotherapy.² Patients with T-cell ALL, infants and adolescents diagnosed with ALL, and those with Philadelphia-chromosome positivity (Ph+) have historically had a poor prognosis and are considered high-risk (HR).² These HR patients need more aggressive treatment regimens than the typical pediatric ALL patient who is usually between the ages of 1 and 9 years old.²

Pediatric ALL is the most common malignancy diagnosed in children with the peak incidence in children aged 2-5 years.⁵ It accounts for nearly 1/3 of all pediatric cancer leading to about 2500-3500 new pediatric ALL diagnoses annually in the United States.⁵ The exact cost of treatment for ALL patients has not yet been identified; however, it has been determined that the

addition of stem cell transplantation (SCT) to traditional chemotherapeutic regimens results in longer hospital stays and increased health care costs.⁴ The precise number of health care visits each year for HR pediatric ALL patients is also not identified at this time, but is documented that more than 40,000 children undergo treatment for childhood cancer each year.³ The exact cause of pediatric ALL remains largely unknown; however, few cases have been linked to associated inherited genetic syndromes (i.e. Down's Syndrome), various viruses (i.e. prenatal exposure to influenza or varicella), and certain environmental factors (i.e. exposure to ionizing radiation).⁵ It is known that with improvements in diagnosis and treatment, overall cure rates for children with ALL approach 80%.⁵

The gold standard for pediatric ALL treatment involves various chemotherapeutic regimens alone using a risk-based approach taking into account the prognostic factors previously mentioned. HR patients are often recommended to receive an allogeneic SCT, which is a controversial topic in this field of medicine since the SCT process can be extremely toxic for a child to endure involving very high doses of chemotherapy and sometimes radiation therapy prior to SCT. The method of treatment involving chemotherapy plus allogeneic SCT is being proposed for HR pediatric ALL patients in an effort to find a therapeutic approach that can improve the overall cure rate for this vulnerable patient population without causing a significant increase in mortality and morbidity rates.

OBJECTIVE

The objective of this selective EBM review is to determine whether or not allogeneic SCT of HR pediatric ALL patients is more effective in preventing future relapses of disease and/or mortality in comparison with chemotherapeutic regimens alone.

METHODS

All three studies in this review were randomized controlled trials (RCT) and required a population of pediatric ALL patients considered to be HR with each study using varying criteria to make this determination. Two out of the three also involved HR pediatric ALL patients enrolled on specific clinical trials such as ALL-BFM 90 and 95 and ALL-REZ BFM 90 (please refer to **Table 1** for more details regarding these studies). Each study in this review differed in terms of the exact treatment protocol they used and evaluated, but all of them involved a variety of chemotherapeutic regimens and allogeneic SCT. The comparison group in all studies involved various subgroups of HR pediatric ALL patients receiving chemotherapeutic regimens alone. All outcomes analyzed qualified as patient oriented evidence that matters (POEM) and included looking at incidence of recurrent disease and/or mortality in HR pediatric ALL patients.

A detailed search using PubMed was completed by the author using key words such as allogeneic stem cell transplantation; acute lymphoblastic leukemia; and pediatric. All articles were in English and published in a peer reviewed journal (Journal of Clinical Oncology) between 2006 and 2010. The author of this selective EBM review conducted the research of the articles used and articles were selected based on the importance of outcomes in patients (i.e. POEMS) and on their relevance to the topic question. Inclusion and exclusion criteria varied amongst the three studies in this review and are outlined in **Table 1**. The summary of statistics reported and/or used include p-values, 95% confidence intervals (CI), various probabilities, and number needed to harm (NNH).

Table 1- Demographics & Characteristics of included studies

Study	Type	# Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Schrauder ⁷ , 2006	Randomized Controlled Trial	179	0-18	Pediatric oncology pts up to 18 yrs old enrolled onto the ALL-BFM 90 and 95 on treatment of childhood ALL in 96 participating centers in Germany, Austria, and Switzerland studies in Germany, Austria, and Switzerland	N/A	0	Various chemotherapeutic regimens alone vs. Allogeneic stem cell transplantation
Ribera ⁶ , 2007	Randomized Controlled Trial	106	0-18	Pediatric high-risk ALL pts who are: -Age younger than 1 year -WBC count $\geq 300 \times 10^9/L$ in B-lineage ALL -WBC count $\geq 100 \times 10^9/L$ in T-lineage ALL -t(9;22), t(4;11), or other 11q23 rearrangements; can also qualify if they have a slow or partial response to induction therapy protocols	Patients who did not achieve complete remission after receiving the first cycle of early intensification chemotherapy	11	Various chemotherapeutic regimens alone divided into various phases (i.e. induction; early intensification 1, 2, and 3; delayed intensification 1,2, and 3); Allogeneic and autologous stem cell transplantation
Tallen ⁹ , 2010	Randomized Controlled Trial	525	0-18	Pediatric oncology patients with first relapse of T- or B- cell precursor Acute Lymphoblastic Leukemia (ALL) younger than 19 years of age; Patients enrolled on trial ALL-REZ BFM 90, which was conducted in 80 hospitals that recruited all children with relapsed ALL in Germany, Austria, and selected centers in Switzerland, the Netherlands, Denmark, and Russia after approval by each local ethics committee	N/A	0	Alternating short-course intensive polychemotherapy and cranial/ craniospinal irradiation followed by maintenance therapy; Allogeneic Stem cell transplantation

OUTCOMES MEASURED

In the study by Schrauder et al., the HR group of patients were defined as the following: prednisone poor response (PPR; $\geq 1,000$ blasts/ μL in peripheral blood after 1 week of prednisone and one intrathecal dose of methotrexate), nonresponse on day33 (NRd33; $\geq 5\%$ blasts in bone marrow on day 33), or positivity for translocations (i.e. t(9;22) or t(4;11) or MLL/AF4 or

BCR/ABL rearrangement).⁷ The outcomes measured in this study were overall survival (OS) rate and mortality rate for this subgroup of patients and were measured by comparing a group of HR patients who received chemotherapy alone (different regimens were used in ALL-BFM 90 compared to ALL-BFM 95) to a group that received allogeneic SCT. The authors of this study monitored very specific outcomes including duration of event-free survival (EFS) and duration of disease-free survival (DFS). EFS is defined as the times from diagnosis until the date of the first event (i.e. relapse, death from any reason, secondary malignancy), or if no such event occurred, until the date of the last contact. DFS involved patients who achieved remission and was defined as the time from complete remission (CR) until the date of the first event (as stated above).⁷

In the study by Ribera et al., improvement of prognosis for HR pediatric ALL patients and their mortality rates were the identified outcomes chosen to be analyzed (refer to **Table 1** for HR criteria).⁶ This study particularly evaluated the outcomes of patients who achieved CR after receiving the first cycle of early intensification therapy. These patients were divided into two groups with one group receiving allogeneic SCT (if they had an HLA-identical sibling donor) and compared to a group of patients who received delayed intensification chemotherapy followed by maintenance treatment. The authors of this study measured the outcomes by specifically monitoring the DFS (calculated from the date of CR until the date of first relapse, death by any cause, or the last follow-up for patients alive in first CR) and OS (measured from the time of entry in the protocol to the time of death or last follow-up).⁶

Tallen et al., authors of the final study in this review, particularly looked at pediatric ALL patients with first relapse of T-or B- cell precursor ALL younger than 19 years of age who were enrolled on the ALL-REZ BFM 90 trial.⁹ The outcomes they chose to evaluate were

improvement of prognosis to ensure EFS and OS. The patients were stratified into three subgroups based on the specific characteristics of their relapse along with a poor prognosis group (PPG) who had very early bone marrow relapse or any relapse of T-cell lineage. The progress on treatment of each patient subgroup was closely monitored for incidences of relapse.⁹

RESULTS

In the study conducted by Ribera et al., patients deemed eligible (n=100) for the study were divided into various subgroups according to the HR category that they identified with (i.e. Infant ALL, ALL with specific cytogenetic translocations, B-lineage ALL without specific rearrangements, T-cell ALL, and slow/ partial responders to induction therapy) and were analyzed as such.⁶ Each subgroup of HR pediatric ALL patients had a set of patients that were randomized to receive an allogeneic SCT if they had an HLA-matched sibling donor (MSD) and a number of patients in that subgroup were randomly assigned to receive chemotherapy alone without SCT. Of the 100 eligible patients, 24 were randomly assigned to receive allogeneic SCT and 38 were randomized to receive chemotherapy without SCT. In the analysis of subgroups, 17 patients actually received an allogeneic SCT (4 patients relapsed before transplant time and 3 moved to the chemotherapy group) and 38 received chemotherapy alone. Amongst the patient subgroup that received allogeneic SCT, 9 out of 17 remained in CR compared to 18 out of 38 in the group that received only chemotherapy. Out of the slow/partial responders to induction therapy group, 7 out of 12 receiving SCT remained in CR compared to 10 out of 21 who received chemotherapy alone. Overall, when the intervention group was compared to the control group, there were no significant differences in DFS for any subgroup (DFS probabilities=40% for SCT and 47% for chemotherapy).⁶ The intention-to-treat analysis in this study also showed no difference in the overall effects of each subgroup when comparing the groups that received an

allogeneic SCT versus those that only received chemotherapy (**Table 2**).⁶ It was concluded that their OS and DFS did not significantly differ from those of patients who received chemotherapy alone. In summary, at the end of the trial there were 10 patients alive in CR out of 24 that were assigned to receive an allogeneic SCT and 15 alive out of 38 who were assigned to receive chemotherapy alone.⁶

Table 2- Statistical Analysis of the Comparison of DFS, OS, and Relapse Probability for Patient Subgroups (i.e. donor vs. no donor/ patients who received chemotherapy alone)

	Variable	# of pts	Median Yrs. F/U	Median (Years)	95% CI	5-Year Probability	5-Year 95% CI
OS							
	Donor/ SCT	24	7.5	3.0	NC	48	30-67
	Chemotherapy	38	5.9	NA	NC	57	43-73
DFS							
	Donor/ SCT	24	7.5	1.4	NC	45	27-65
	Chemotherapy	38	5.8	2.9	NC	46	32-62
Relapse probability							
	Donor/SCT	22	6.8	NA	NC	33	12-56
	Chemotherapy	36	5.4	NA	NC	47	31-61

**OS- Overall Survival; DFS- Disease-Free Survival; Relapse Probability- from beginning of late intensification therapy; NA- Not achieved; NC- Not Computable

The study by Schrauder et al., involving clinical trials ALL-BFM 90 and 95, deemed 191 of 4,347 patients eligible to receive a MSD-SCT because of PPR and/or NRd33 (104 patients in ALL-BFM 90 and 87 patients in ALL-BFM 95).⁷ 36 out of 76 patients who reached CR received an SCT. In ALL-BFM 90, 10 patients received a MSD-SCT and 86 patients were treated with chemotherapy alone. An adjustment was made for a minimum follow-up of 0.43 years post diagnosis, which was the medium time to transplantation. This adjustment resulted in a DFS rate at 5 years of 35% +/- 6% for the patients treatment with chemotherapy alone and 50% +/- 16% for the patients who received SCT (P=.27).⁷ 57 out of 83 patients in the ALL-BFM 95 trial were treated with chemotherapy alone and 26 patients received SCT. In this trial, they also used matched unrelated donors (MUD) and mismatched family donors (MMFD) and the results

amongst these patient subgroups were further analyzed. These groups were combined to enhance the overall effect of further analysis. There was no significant difference when comparing the DFS rate at 5 years of the SCT and chemotherapy groups in ALL- BFM 95 (P=.09). Overall, for both treatment regimens (SCT vs. chemotherapy alone) results were better in the ALL-BFM 95 trial; however, both trials were able to demonstrate a statistically significant difference in the DFS at 5 years between the control and intervention groups indicating that allogeneic SCT significantly improved the results achieved by chemotherapy alone (DFS at 5 years, 67% +/- 8% v. 42% +/- 5%, respectively; P=.01).⁷ OS at 5 years also yielded similar results with the same statistics previously mentioned for DFS.⁷ There was a significant decrease in relapse incidence between the two trials in this study (69% +/- 5%, 59 of 86 patients; 46% +/- 8%, 26 of 57 patients; P= .004) for the patients who received chemotherapy alone.⁷ On the other hand, there was an increase in the incidence of death for patients in CR within the same subgroup (**Table 3**). For patients who received SCT, there was a difference in relapse incidence amongst the MSD-SCT and MUD/MMFD-SCT subgroups (MSD-SCT=8 of 23 patients; MUD/MMFD-SCT=0 of 13 patients; P=.0001).⁷ Please refer to **Table 3** for specific adverse effects in this patient group.⁷ The number needed to harm (NNH) in this study was calculated to be 17 patients.

Table 3- Adverse Effects: HSCT vs. Chemotherapy Alone Subgroups

	Variable	# of Pts	Deaths	Other Adverse Events	P-Values
ALL-BFM 90	SCT	10	-	-	.09
	Chemotherapy	86	2*	-	
ALL-BFM-95	SCT	36	4**	-	.001
	Chemotherapy	57	5*	1***	

*Deaths included- (both trials combined)- 4 from infection, 1 from cerebral hemorrhage, and 2 from thromboembolism

**Deaths included- (occurred only after MUD/MMFD-SCT in ALL-BFM 95)- 2 from infection, 1 from infection plus graft failure, and 1 from veno-occlusive disease plus multiorgan failure

***Other adverse events- 1 secondary malignancy

The final study by Tallen et al., had a total of 525 participants that were further divided into three subgroups (A-early bone marrow (BM) relapses, B- late BM relapses, C- isolated extramedullary relapses, and PPG- poor prognosis group) based on their specific HR prognostic characteristics.⁹ Out of the 525, 323 patients received chemoradiotherapy alone and 117 received SCT (87 of the 117 were allogeneic SCT). SCT significantly improved the probability of EFS (pEFS) in the HR patient group (groups A and PPG: n=84; pEFS= 33% +/- 5%; and HLA-compatible allogeneic grafts only: n=53; pEFS= 40% +/- 7%) as compared to chemotherapy alone (n=76; pEFS= 20% +/- 5%; P <.005 or <.001, respectively).⁹ Tallen further analyzed the individual prognostic factors and in a multivariate Cox regression analysis SCT as a time-dependent covariate (risk ratio for subsequent event after SCT v. chemotherapy alone, 1 v. 1.8, P <.001) proved to be an independent predictor of EFS.⁹

An analysis of adverse effects of the intervention (allogeneic SCT) was difficult in this study since post-remission therapy events were documented according to the subgroups (A, B, C, and PPG) and the patients who only received allogeneic SCT were not separated out of these groups. For purposes of this review, the post-remission therapy events for Groups A and PPG will be noted since they each had more patients receive SCT as compared to Groups B and C.⁹ A breakdown of such events are listed in **Table 4**.⁹ Overall, the NNH in this study was calculated to be 5 patients.

Table 4- Adverse Events of Trial ALL-REZ BFM 90: Groups A and PPG

	Group A	Group PPG
# of pts who received chemoradiotherapy	60	60
# of pts who received SCT	45	39
Induction Death	7	12
Non-Response	14	41
Treatment-related Death	13	9
Subsequent Relapse	69	67
Secondary Malignancy	2	1

DISCUSSION

The three studies discussed in this selective EBM review all investigated the potential benefits of adding SCT to the treatment regimen of HR pediatric ALL patients; however, each had different variables that significantly affected their outcomes. In Schrauder's study, they compared the outcomes of HR-T-ALL patients who received allogeneic SCT with those of patients who received chemotherapy alone further analyzing the outcomes of SCT patients according to the type of donor finding that relapses only occurred after MSD-SCT and not the other subgroup; however, the low number of events did not allow for definite conclusions despite the statistically significant difference. This study was the first to demonstrate that SCT in CR1 had superior outcomes when compared to chemotherapy alone.⁷

Tallen et al. assessed the impact of SCT for experimental post-remission treatment in HR patients discovering that second CR rates and pEFS were significantly higher after allogeneic SCT than after chemoradiotherapy alone in HR, but not in intermediate-risk patients. They also demonstrated that various prognostic factors (i.e. time point, site of relapse, ALL immunophenotype, and SCT time-dependent covariate) proved to all be independently associated with EFS in this trial and helped identify a stratification system that was used to determine the different subgroups that were analyzed in this study so that more specific treatment recommendations could be made. This risk-based approach also helped them to determine that allogeneic SCT should be recommended as a treatment option for the PPG patient subgroup in ongoing trials.⁹

In contrast to the two previous studies mentioned above, the trial by Ribera et al. failed to prove that allogeneic SCT provides a better outcome than chemotherapy alone in children with VHR-ALL in first CR. There were limitations in this trial such as the low frequency of VHR

patients, specifically those who have certain chromosomal translocations making it difficult to draw any definite conclusions in regards to the benefit of SCT in this population. Another limitation involved the time frame between achievement of CR and the beginning of the patient's assigned therapy (i.e. SCT or chemotherapy alone). The patients assigned to SCT experienced a longer time frame than the patients who only received chemotherapy. There was also a lack of strict rules for the preparative regimen prior to SCT also making it difficult to draw definitive conclusions. Despite the various concerns in this study, the overall outcomes achieved in this trial confirmed that the prognosis of VHR pediatric ALL patients remains poor even with the addition of SCT.⁶

CONCLUSION

After reviewing the three articles discussed in this selective EBM review, the evidence is inconclusive and conflicting as to whether or not the addition of allogeneic SCT improves overall outcomes for HR pediatric ALL patients as compared to receiving chemotherapy alone. Each study in this review had very different and specific criteria that they used in determining patients HR, which influenced the results of the study making it difficult to identify definitive conclusions regarding the addition of SCT. This area of research should definitely continue since some of the studies did show positive outcomes when SCT was added; however, these studies are limited in number. There is also room for this specific area of research to be conducted more in the United States since the studies in this review were conducted in Europe. In summary, the prognosis of HR pediatric ALL patients has historically been poor, but the use of allogeneic SCT has proven some benefit despite its risks. With this in mind, the need for ongoing research of this specific therapeutic intervention is absolutely imperative in an attempt to improve the overall survival of the HR pediatric ALL patient population.

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