

Review Article

Isolated Extramedullary Relapse of Pediatric Leukemia Following Stem Cell Transplantation: A Single Center Review

Travis W Dum^{1,2}, Karen Effinger^{1,2}, Shannon Witty^{1,2}, Jingnan Mao², Yvonne Barnes³, Shalini Shenoy^{1,2} and Robert J Hayashi^{1,2*}

¹Division of Pediatric Hematology-Oncology, Washington University School of Medicine, USA

²Department of Pediatrics, Washington University School of Medicine, USA

³St. Louis Children's Hospital, USA

Corresponding author

Robert J Hayashi, Division of Pediatric Hematology/Oncology, Department of Pediatrics, Washington University School of Medicine. 660 South Euclid Ave. St. Louis, Missouri, 63110 USA, Tel: 314-454-6018; Fax: 314-454-2780; Email: hayashi_r@kids.wustl.edu

Submitted: 26 October 2013

Accepted: 12 November 2013

Published: 05 June 2014

ISSN: 2333-6684

Copyright

© 2014 Hayashi et al.

OPEN ACCESS

Keywords

- Extramedullary
- Recurrence
- Stem cell transplantation

Abstract

Leukemic Extramedullary (EM) relapse is now more common than once reported, but experiences beyond case studies are limited in the pediatric literature. We conducted a retrospective review of 115 transplant procedures in leukemia patients performed at our institution over a 16-year period. Our analysis revealed an overall post transplant relapse rate of 37% (n=43), with 19% (n=8) of those relapses occurring in isolated extramedullary sites.

Patients whose initial post transplant relapse was in an EM site were found to survive 14 months longer than patients who relapsed in the bone marrow (BM) (p=0.012). EM relapse also proved to be significantly associated with the presence of chronic graft-versus-host disease (GVHD) and the presence of both acute and chronic GVHD when compared to the BM relapse group (p=0.046 and p=0.037). Of the patients with EM relapse, 37.5% of the patients are still surviving with salvage therapy compared to 14.3% of patients who have relapsed in the BM. Our results indicate that EM relapse represents a significant source of failure for pediatric patients with leukemia undergoing allogeneic transplantation, but long term survival can be achieved. Further studies characterizing this population and developing new salvage treatments for these patients may improve their survival.

INTRODUCTION

Allogeneic Stem Cell Transplant (SCT) has proven to be an effective treatment for patients with high risk leukemia. However, leukemic relapse continues to be the common cause of mortality following transplant [1-2]. Although the Bone Marrow (BM) is the most frequent site of recurrence, Extramedullary (EM) relapse does occur and has been reported with varying frequencies at different institutions. Lee et al reported that up to 50% of post transplant relapses contained an extramedullary component in their population [3]. Yet most of the literature on this topic consists of case reports and there are few studies examining the risk factors for EM relapse in the post transplant setting. The published experience in the pediatric population is even more limited. With allogeneic stem cell transplantation

the preferred treatment for recurrent leukemia, extramedullary relapses will invariably increase in number as the number of procedures increases annually. In order to further characterize the occurrence of initial EM leukemic relapse post-SCT in a larger pediatric population, we conducted a retrospective review of 115 transplants in pediatric leukemia patients performed at our institution.

PATIENTS AND METHODS

Patients

Between September 1991 and May 1, 2007, 111 patients with leukemia underwent 115 allogeneic Stem Cell Transplants (SCT) at St. Louis Children's Hospital, and the Washington University School of Medicine. 9 of those patients also received Donor

Lymphocyte Infusions (DLI). Of these 124 infusions, 7 were excluded from evaluation of relapse due to lack of engraftment or persistent disease after transplant. The remaining 117 procedures were evaluated in a retrospective chart review. All patients who experienced an initial extramedullary relapse or bone marrow relapse following the transplant procedure were identified. Extramedullary relapse was defined as a pathologically documented recurrence of disease occurring at any time after the transplant procedure without recurrence at the same time in the bone marrow. Patients with bone marrow recurrence developing subsequent to the extramedullary recurrence were included in

the analysis. Two events were excluded due to simultaneous relapse both in the bone marrow and at an extramedullary site, leaving a population of 115 procedures in 104 patients (Table 1).

Clinical data

Information on the 115 procedures was collected retrospectively from the patients' medical records and included data up to July 5, 2007. The following data was recorded: date of birth, diagnosis, date of transplant, type of donor, donor compatibility, preparative regimen, presence of acute or chronic GVHD, date of relapse, site of relapse, and date of death.

Table 1: Patient Characteristics.

	Total Population		Relapses			
		Rate	Bone Marrow	Rate	Extramedullary	Rate
Total Events	115		35	30.4%	8	7.0%
<i>Male</i>	74	64.3%	20	57.1%	6	75.0%
<i>Female</i>	41		15		2	
Diagnosis						
<i>ALL</i>	64	55.7%	22	62.9%	6	75.0%
<i>AML</i>	41	35.7%	10	28.6%	1	12.5%
<i>CML</i>	6	5.2%	1		0	
<i>JMML</i>	4	3.5%	2		1	
Type of Event						
<i>Stem Cell Transplant</i>	109		34		6	
<i>DLI</i>	6		1		2	
Age at Transplant						
<i>Average</i>	9.9		9.8		6.7	
<i>Range</i>						
<i>Median</i>	9.2		8.5		6.0	
Stem Cell Source						
<i>MUD</i>	56	48.7%	16	45.7%	4	50.0%
<i>Sibling</i>	53	46.1%	16	45.7%	4	50.0%
<i>Cord</i>	3		1		0	
Preparative Regimen						
<i>SDTBI/Cytoxan</i>	58		21		3	
<i>Busulfan/Cytoxan</i>	11		5		1	
<i>Ara-C/Cytoxan/TBI</i>	8		0		0	
<i>Cytoxan/TBI/VP-16</i>	8		0		0	
<i>Cytoxan/TBI</i>	7		3		0	
<i>TBI/VP-16</i>	6		2		0	
<i>DLI</i>	7		1		2	
<i>Thiotepa/ATG/TBI/Cytoxan</i>	3		1		0	
<i>Busulfan/Cytoxan/VP-16</i>	3		0		1	
<i>ATG/Cytoxan</i>	2		1		1	
<i>Busulfan/Melphalan/ATG</i>	2		0		0	
<i>Cytoxan/ATG/TBI</i>	2		1		0	
GVHD	50	43.5%	11	31.4%	5	62.5%
<i>acute</i>	31	27.0%	5	14.3%	4	50.0%
<i>chronic</i>	16	13.9%	2	5.7%	3	37.5%
<i>acute and chronic</i>						
Status						
<i>Dead</i>	60	52.2%	30	85.7%	5	62.5%
<i>Alive</i>	55	47.8%	5	14.3%	3	37.5%

Preparative regimens varied with diagnosis, the prevailing protocol that was available, and physical status of the patient, as did the treatment for the recurrent disease. The following preparative regimens were utilized during the 16 year period in review: Ara-C/Cytosin/TBI [4], ATGAM/Cytosin [5], Busulfan/Cytosin [6], Busulfan/Cytosin/VP-16 [7], Busulfan/Melphalan/ATGAM [8],

Cytosin/ATGAM/TBI [9], Cytosin/TBI [10], Cytosin/TBI/VP-16 [11], SDTBI/ Cytosin [12], TBI/VP-16 [13], Thiotepa/ATGAM/TBI/ Cytosin [14] (Table 1). The presence of clinical GVHD was diagnosed according to previously established criteria, and when needed, tissue biopsies were obtained to confirm the diagnosis [15,16]. Disease relapse was also confirmed by biopsy. Bone Marrow (BM) relapse was defined as greater than 5% blasts upon bone marrow examination at any time after the transplant procedure. Extramedullary relapse (EM) was defined by the presence of leukemic cells in any body compartment outside of the bone marrow. EM relapse in the bone was defined as a focal site of bone, pathologically proven to be involved with leukemia in the absence of bone marrow involvement assessed by standard bone marrow aspirations and biopsies. Post-transplant relapses were treated and included cytotoxic chemotherapy, Donor Leukocyte Infusions (DLI), radiation, surgery, and subsequent transplant following myeloablative or reduced intensity conditioning.

Statistical methods

Differences in time to relapse, time to death, and time from relapse to death between the EM relapse group and the BM relapse group were detected using the Wilcoxon Rank Sum test. The Chi-square test and Fisher's exact test were used to detect the association of presence of acute and chronic GVHD, the type of disease, and the two relapse groups. P value of 0.05 was set as the significance level.

RESULTS AND DISCUSSION

Results

Table 1 provides a summary of the demographic data. The average age at transplant was 9.9 years and the ratio of males to females was 1.8:1. Acute lymphoblastic leukemia (ALL) was the diagnosis in 64 (56%) of the patients with 41 (36%), 6 (5%), and 4 (4%) patients with the diagnosis of Acute Myelogenous Leukemia (AML), chronic myelogenous leukemia (CML), and Juvenile Myelomonocytic Leukemia (JMML), respectively. Of the 115 total procedures, 43 (37%) resulted in relapse. 81% (n=35) of the 43 initial, isolated post-transplant relapses occurred in the bone marrow and 19% (n=8) occurred in extramedullary sites. 75% (n=6) of the patients who relapsed at EM sites were diagnosed with ALL, however this was not statistically significant (p=0.65) when compared to the 63% (n=22) of BM relapse patients diagnosed with ALL. Sex, stem cell source, and preparative regimen were not associated with relapse.

Individual characteristics for patients who relapsed in EM sites can be found in Table 2. Testicular disease was the most common site of EM relapse, accounting for 4 of the 8 relapses. Subsequent relapse in the BM occurred in 3 of the 8 initial EM relapse patients (Patients 28, 105, 109, 153) and 2 of the 8 patients (225, 273) relapsed at EM sites different from their initial

relapse. 1 patient (153) relapsed in both the BM and another EM site after an initial isolated testicular relapse.

The average time from transplant to relapse was 184 days for patients who relapsed in the BM, and 244 days for patients who relapsed in EM sites (Table 3). This difference in time to relapse was not found to be statistically significant (p=0.26). However, the time intervals from transplant to death and from relapse to death were found to be significantly longer for the EM relapse group compared to the BM relapse group (p=0.012, p=0.010). On average, the time from relapse to death was 206 days for the BM relapse group and 637 days for the EM relapse group. Time from transplant to death for patients who relapsed in the BM was 379 days compared to 936 days for patients who relapsed in EM sites. The presence of acute GVHD did not prove to be significantly different (p=0.1) between the two groups. However, patients who experienced EM relapses were more likely to have had chronic GVHD (p=0.046) or both acute and chronic GVHD (p=0.037).

Discussion

The most frequent site of relapse following allogeneic stem cell transplant is in the Bone Marrow (BM), but several studies have shown that up to 50% of all leukemic relapses involve Extramedullary (EM) sites [3,17-21] and that 5-27% of all initial relapses occur in extramedullary sites without BM involvement [3,16-18,20-23]. Single center reviews of the adult leukemia population have shown that a longer time interval between transplant and relapse is associated with EM leukemic relapse post-transplant, and that the effects of Graft-Versus-Host Disease (GVHD) are not the same between EM relapses and BM relapses [3,16,17,22]. These findings suggest that the Graft-Versus-Leukemia (GVL) effect may not be as effective in controlling disease in extramedullary sites as in the bone marrow. Yet the characteristics of EM relapse have not been adequately reported in the pediatric population.

Our data revealed that the overall leukemic relapse rate of 37% in our population is consistent with the rate of relapse following transplant in the pediatric leukemia population. The 19% EM relapse rate at our institution is also within the reported incidence of 5-27% by other centers.

GVHD has been associated with a decreased incidence of relapse and longer relapse-free survival post-transplant presumably due to the GVL effect [24]. We found that relapses at EM sites, compared to BM relapse, were significantly associated with the presence of chronic GVHD and the presence of both acute and chronic GVHD. Acute GVHD has proven to be effective in preventing relapse [24,25], but our review, along with others, reveals that GVHD is less effective in preventing EM relapse [16,26].

A popular hypothesis is that some EM sites may act as sanctuary sites, or immune privileged spaces for the tumor cells, protecting them from systemic therapy and potential GVL effects [26-33]. With 5 out of 8 of the EM relapses (UPN 28, 109, 153, 200, 273) at our institution occurring in well known sanctuary sites such as the testes and central nervous system, this explanation is supported by our data. However, relapses at EM sites other than the typical sanctuary sites are frequently reported [34].

Testicular relapse accounted for 4 out of 5 sanctuary site relapses and 50% of all initial post-transplant EM relapses experienced at our institution. Of the 4 patients who experienced testicular relapse, 3 received conditioning consisting of single dose TBI and Cytoxan. Quaranta et al reported on their experience with Total Body Irradiation (TBI) and testicular boost prior to SCT, which resulted in primary testicular relapse in 4.2% of the patients [35]. They suggested the need of adding a testicular boost to TBI based regimens in order to prevent testicular relapse. However, the 3 patients in our population who relapsed in the testicles following the single dose TBI regimen only represent 7.7% of the males who received the same conditioning regimen in our study. This number is not significantly different compared to the overall EM relapse rate of 7.0% in our population to make any claims about a specific conditioning regimen contributing to the risk of relapse. In their review of 207 cases of EM relapse, Cunningham et al were unable to define the role of conditioning regimens [34].

Our data also revealed that patients who relapsed in EM sites survived 14 months longer than patients who relapsed in the BM. This finding is consistent with other studies and is especially significant in the pediatric population in which the average age at transplant at our institution is 10 years old. Some studies have suggested that this improved survival time is due to a longer time interval from transplant to relapse in EM relapse patients, which allows for more intensive treatment [16]. However, our numbers revealed that EM relapses did not occur significantly later than BM relapses (Table 3). While the overall survival outcome between the two groups was similar, the longer survival time of EM relapse patients suggests that these patients can potentially achieve a better outcome.

Our study is limited in that its retrospective nature. Our strict definition of isolated EM relapse as the initial relapse post transplant without concurrent BM disease reduced the number of patients we reviewed. Although our population size of 115 procedures is a considerable number relative to other pediatric studies on this subject, a larger cohort of patients would be beneficial to further elucidate the factors involved in EM relapse. Despite previous reports examining larger numbers of EM relapses from several centers [34], the nature of our report allows us to define the characteristics of patients experiencing EM relapse. Our study involved all of the patients receiving an allogeneic SCT for pediatric leukemia at a single institution. Unlike previously published literature reviews, we were able to obtain detailed clinical information for all subjects and had pathological proof of EM relapses. These factors allowed us to more accurately define the incidence of post-transplant EM relapse, which has previously been underreported or reported mainly in the form of case studies. Given that we observed that 19% of all initial post transplant relapses at our institution were EM relapses, this clinical entity is an important issue regarding that has implications for post transplant disease monitoring and the ultimate outcome of this population. With stem cell transplants now a standard treatment for recurrent leukemia, more prospective studies are needed in order to better understand this condition and potentially improve the outcome of this patient population.

CONCLUSION

Extramedullary relapse represents a significant source of failure for pediatric patients with leukemia undergoing allogeneic transplantation, but long-term survival can be achieved and may be at a higher rate than those patients who relapse from the bone marrow. Further studies characterizing this population and developing new salvage treatments for these patients may further improve their survival.

REFERENCES

1. Giralt SA, Champlin RE. Leukemia relapse after allogeneic bone marrow transplantation: a review. *Blood*. 1994; 84: 3603-3612.
2. Frassoni F, Barrett AJ, Grañena A, Ernst P, Garthon G, Kolb HJ, et al. Relapse after allogeneic bone marrow transplantation for acute leukaemia: a survey by the E.B.M.T. of 117 cases. *Br J Haematol*. 1988; 70: 317-320.
3. Lee KH, Lee JH, Kim S, Lee JS, Kim SH, Kim WK. High frequency of extramedullary relapse of acute leukemia after allogeneic bone marrow transplantation. *Bone Marrow Transplant*. 2000; 26: 147-152.
4. Riddell S, Appelbaum FR, Buckner CD, Stewart P, Clift R, Sanders J, et al. High-dose cytarabine and total body irradiation with or without cyclophosphamide as a preparative regimen for marrow transplantation for acute leukemia. *J Clin Oncol*. 1988; 6: 576-582.
5. Storb R. Preparative regimens for patients with leukemias and severe aplastic anemia (overview): biological basis, experimental animal studies and clinical trials at the Fred Hutchinson Cancer Research Center. *Bone Marrow Transplantation*. 1994; 14: S1-S3.
6. Copelan EA, Biggs JC, Szer J, Thompson JM, Crilley P, Brodsky I, et al. Allogeneic bone marrow transplantation for acute myelogenous leukemia, acute lymphoblastic leukemia, and multiple myeloma following preparation with Busulfan and Cyclophosphamide (BuCy2). *Seminars in Oncology*. 1993; 20: 33-38.
7. Jones RJ, Santos GW. New conditioning regimens for high risk marrow transplants. *Bone Marrow Transplant*. 1989; 4 Suppl 4: 15-17.
8. Martino R, Badell I, Brunet S, Sureda A, Nomdedéu J, Altés A, et al. Second bone marrow transplantation for leukemia in untreated relapse. *Bone Marrow Transplant*. 1994; 14: 589-593.
9. Ringdén O, Remberger M, Persson U, Ljungman P, Aldener A, Andström E, et al. Similar incidence of graft-versus-host disease using HLA-A, -B and -DR identical unrelated bone marrow donors as with HLA-identical siblings. *Bone Marrow Transplant*. 1995; 15: 619-625.
10. Clift RA, Buckner CD, Appelbaum FR, Bearman SI, Petersen FB, Fisher LD, et al. Allogeneic marrow transplantation in patients with acute myeloid leukemia in first remission: a randomized trial of two irradiation regimens. *Blood*. 1990; 76: 1867-1871.
11. Duerst RE, Horan JT, Liesveld JL, Abboud CN, Zwetsch LM, Senf ES, et al. Allogeneic bone marrow transplantation for children with acute leukemia: cytoreduction with fractionated total body irradiation, high-dose etoposide and cyclophosphamide. *Bone Marrow Transplant*. 2000; 25: 489-494.
12. Girgis M, Hallemeier C, Blum W, Brown R, Lin HS, Khoury H, et al. Chimerism and clinical outcomes of 110 recipients of unrelated donor bone marrow transplants who underwent conditioning with low-dose, single-exposure total body irradiation and cyclophosphamide. *Blood*. 2005; 105: 3035-3041.
13. Dopfer R, Henze G, Bender-Gotze C, Ebell W, Ehninger G, Friedrich W, et al. Allogeneic bone marrow transplantation for childhood acute

- lymphoblastic leukemia in second remission after intensive primary and relapse therapy according to the BFM- and CoALL-protocols: results of the German cooperative study. *Blood*. 1991; 78: 2780-2784.
14. Bacigalupo A, Lamparelli T, Gualandi F, Bregante S, Raiola AM, Grazia CD, et al. Prophylactic antithymocyte globulin reduces the risk of chronic graft-versus-host disease in alternative-donor bone marrow transplants. *Biol Blood Marrow Transplant*. 2002; 8: 656-661.
 15. Chong G, Byrnes G, Szer J, Grigg A. Extramedullary relapse after allogeneic bone marrow transplantation for haematological malignancy. *Bone Marrow Transplant*. 2000; 26: 1011-1015.
 16. Lee KH, Lee JH, Choi SJ, Lee JH, Kim S, Seol M, et al. Bone marrow vs extramedullary relapse of acute leukemia after allogeneic hematopoietic cell transplantation: risk factors and clinical course. *Bone Marrow Transplant*. 2003; 32: 835-842.
 17. Mehta J, Powles R, Treleaven J, Horton C, Meller S, Pinkerton CR, et al. Outcome of acute leukemia relapsing after bone marrow transplantation: utility of second transplants and adoptive immunotherapy. *Bone Marrow Transplant*. 1997; 19: 709-719.
 18. Michel G, Boulad F, Small TN, Black P, Heller G, Castro-Malaspina H, et al. Risk of extramedullary relapse following allogeneic bone marrow transplantation for acute myelogenous leukemia with leukemia cutis. *Bone Marrow Transplant*. 1997; 20: 107-112.
 19. Mortimer J, Blinder MA, Schulman S, Appelbaum FR, Buckner CD, Clift RA, et al. Relapse of acute leukemia after marrow transplantation: natural history and results of subsequent therapy. *J Clin Oncol*. 1989; 7: 50-57.
 20. Simpson DR, Nevill TJ, Shepherd JD, Fung HC, Horsman DE, Nantel SH, et al. High incidence of extramedullary relapse of AML after busulfan/cyclophosphamide conditioning and allogeneic stem cell transplantation. *Bone Marrow Transplant*. 1998; 22: 259-264.
 21. Lee JH, Choi SJ, Lee JH, Seol M, Lee YS, Ryu SG, et al. Anti-leukemic effect of graft-versus-host disease on bone marrow and extramedullary relapses in acute leukemia. *Haematologica*. 2005; 90: 1380-1388.
 22. Bordigoni P, Esperou H, Souillet G, Pico J, Michel G, Lacour B, et al. Total body irradiation - high dose cytosine arabinoside and melphalan followed by allogeneic bone marrow transplantation from HLA-identical siblings in the treatment of children with acute lymphoblastic leukaemia after relapse while receiving chemotherapy: a Societe Francaise de Greffe de Moelle study. *Br J Haematol*. 1998; 102: 656-665.
 23. Gassas A, Sung L, Saunders EF, Doyle J. Graft-versus-leukemia effect in hematopoietic stem cell transplantation for pediatric acute lymphoblastic leukemia: significantly lower relapse rate in unrelated transplantations. *Bone Marrow Transplantation*. 2007; 40: 951-955.
 24. Ishiyama K, Takami A, Shiobara S, Koizumi S, Nakao S, Kanazawa University Hospital Haematopoietic Stem Cell Transplantation group. Graft-versus-leukemia effect of allogeneic stem cell transplantation; a Japanese single center study. *Haematologica*. 2004; 89: 887-889.
 25. Tringali S, Vasta S, Scimè R, Catania P, Cavallaro AM, Majolino I. Testicular relapse of AML during chronic graft-versus-host disease induced by donor leukocyte infusion. *Haematologica*. 1996; 81: 339-342.
 26. Huck K, Laws HJ, Meisel R, Traeger A, Bernbeck B, Schonberger S, et al. Three cases of renal relapse after allogeneic hematopoietic stem cell transplantation for childhood acute lymphoblastic leukemia. *Haematologica*. 2006; 91: ECR07.
 27. Seo S, Kami M, Honda H, Kashima T, Matsumura T, Moriya A, et al. Extramedullary relapse in the so-called 'sanctuary' sites for chemotherapy after donor lymphocyte infusion. *Bone Marrow Transplant*. 2000; 25: 226-227.
 28. Au WY, Lie AK, Liang R, Kwong YL. Isolated extramedullary relapse of acute lymphoblastic leukaemia after allogeneic bone marrow transplantation. *Bone Marrow Transplant*. 1999; 24: 1137-1140.
 29. Berthou C, Léglise MC, Herry A, Balcon D, Hardy E, Lessard M, et al. Extramedullary relapse after favorable molecular response to donor leukocyte infusions for recurring acute leukemia. *Leukemia*. 1998; 12: 1676-1681.
 30. Choi SJ, Lee JH, Lee JH, Kim S, Seol M, Lee YS, et al. Treatment of relapsed acute myeloid leukemia after allogeneic bone marrow transplantation with chemotherapy followed by G-CSF-primed donor leukocyte infusion: a high incidence of isolated extramedullary relapse. *Leukemia*. 2004; 18: 1789-1797.
 31. Schäfer H, Bader P, Kaiserling E, Klingebiel T, Handgretinger R, Kanz L, et al. Extramedullary relapses at uncommon sites after allogeneic stem cell transplantation. *Bone Marrow Transplant*. 2000; 26: 1133-1135.
 32. Jaing TH, Hung IJ, Shih LY, Yang CP, Hsueh C, Lo WC. Extramedullary relapse in the left proximal femur with Philadelphia chromosome positive acute lymphoblastic leukemia after allogeneic bone marrow transplantation. *Journal of Pediatric Hematology/Oncology*. 2003; 25: 65-68.
 33. Cunningham I. Extramedullary sites of leukemia relapse after transplant. *Leuk Lymphoma*. 2006; 47: 1754-1767.
 34. Quaranta BP, Halperin EC, Kurtzberg J, Clough R, Martin PL. The incidence of testicular recurrence in boys with acute leukemia treated with total body and testicular irradiation and stem cell transplantation. *Cancer*. 2004; 101: 845-850.
 35. Dermime S, Mavroudis D, Jiang YZ, Hensel N, Mollrem J, Barrett AJ. Immune escape from a graft-versus-leukemia effect may play a role in the relapse of myeloid leukemias following allogeneic bone marrow transplantation. *Bone Marrow Transplantation*. 1997; 19: 989-999.

Cite this article

Dum TW, Effinger K, Witty S, Mao J, Barnes Y, et al. (2014) Isolated Extramedullary Relapse of Pediatric Leukemia Following Stem Cell Transplantation: A Single Center Review. *J Hematol Transfus* 2(2): 1016.