Less intensive approaches to cure: The Alberta Children's Hospital Experience with the NIH Nonmyeloablative Protocol

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October 6, 2023

Disclosures/Conflicts of Interest

- bluebirdbio provides financial support for Project Sickle Cure
  - I am the PI of this study
  - I receive no personal remuneration from bbb

En plus…

- Je suis Canadien et le Canada est un pays bilingue
  - J'étudiais en Français jusqu'à l'université, mais mon français n'est pas si fort ces jours…
  - Mes enfants apprennent en Anglais, Français et Espanol
  - Je vous remercie pour avoir l'opportunité de faire cette presentation en Anglais

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Objectives

- To review principles of hematopoietic cell transplantation (HCT)- and why intensity matters
- To present the ACH experience with the NIH regimen describing safety, efficacy and end-organ outcomes
- To discuss future directions with this approach

What is the goal of HCT for SCD?

- What is the definition of cure?
  - **Survival**
  - **Donor hematopoietic cell engraftment to prevent sickling**
  - No hemolysis
  - **No graft-versus-host disease**
  - Minimal impact on quality of life
    - We are trying to make it better!

(Bernaudin et al, Haematologica 2020)

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- Other important goals
  - Minimal acute and long-term complications
    - From the HCT and from SCD
    - Avoid treatment-related neoplasms
      - Genotoxicity and risk of myeloid malignancy
    - **Fertility preservation**

How much donor engraftment is enough?

TRANSPLANTATION

At least 20% donor myeloid chimerism is necessary to reverse the sickle phenotype after allogeneic HSCT

Courtney D. Fitzhugh,[1,2] Stefan Cordes,[3] Tiffani Taylor,[2] Wynona Coles,[2] Katherine Roskom,[1] Mary Link,[2] Matthew M. Hsieh,[2] and John F. Tisdale[2]

[1]Sickle Cell Branch, National Heart, Lung, and Blood Institute (NHLBI), [2]Molecular and Clinical Hematology Branch, National Institute of Diabetes and Digestive and Kidney Diseases/NHLBI, and [3]Hematology Branch, NHLBI, National Institutes of Health, Bethesda, MD

ELSEVIER

Biology of Blood and Marrow Transplantation

Available online 4 September 2017

In Press, Corrected Proof

Relationship between Mixed Donor–Recipient Chimerism and Disease Recurrence after Hematopoietic Cell Transplantation for Sickle Cell Disease

Allistair Abraham [1], Matthew Hsieh [2, 3], Mary Eapen [4] ✉, Courtney Fitzhugh [2, 3], Jeanette Carreras [4], Daniel Keesler [4], Gregory Guilcher [5], Naynesh Kamani [6], Mark C. Walters [7], Jaap J. Boelens [8], John Tisdale [2, 3], Shalini Shenoy [9], National Institutes of Health, Center for International Blood and Marrow Transplant Research

(Fitzhugh et al, Blood 2017; Abraham et al, Biol Blood Marrow Transplant 2017)

Minimum chimerism

- 20-25% to prevent sickling crises
  - (Whole blood testing)
  - Many children who receive myeloablation still have mixed chimerism
- 25-50% donor chimerism can result in hemolytic markers without sickling crises and Hb S <50%

Vol. 105 No. 1 (2020): January, 2020 > Long-term event-free survival, chimerism and fertility...

ARTICLES

Long-term event-free survival, chimerism and fertility outcomes in 234 patients with sickle-cell anemia younger than 30 years after myeloablative conditioning and matched-sibling transplantation in France

Françoise Bernaudin, Jean-Hugues Dalle, Dominique Bories, Regis Peffault de Latour, Marie Robin, Yves Bertrand, Corinne Pondarre, Jean-Pierre Vannier, Benedicte Neven, Mathieu Kuentz, Sébastien Maury, Patrick Lutz, Catherine Paillard, Karima Yakouben, Isabelle Thuret, Claire Galambrun, Nathalie Dhedin, Charlotte Jubert, Pierre Rohrlich, Jacques-Olivier Bay, Felipe Suarez, Nicole Raus, Jean-Paul Vernant, Eliane Gluckman, Catherine Porrot, Gérard Socié, for the Société Française de Greffe de Moelle et de Thérapie Cellulaire

Vol. 105 No. 1 (2020): January, 2020 https://doi.org/10.3324/haematol.2018.212207

(Bernaudin et al, Haematologica 2020)

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CLINICAL GUIDELINES

blood advances

American Society of Hematology 2021 guidelines for sickle cell disease: stem cell transplantation

Julie Kanter,[1] Robert I. Liem,[2] Françoise Bernaudin,[3,4] Javier Bolaños-Meade,[5] Courtney D. Fitzhugh,[6] Jane S. Hankins,[7] M. Hassan Murad,[8] Julie A. Panepinto,[9] Damiano Rondelli,[10] Shalini Shenoy,[11] John Wagner,[12] Mark C. Walters,[13] Teonna Woolford,[14] Joerg J. Meerpohl,[15,16] and John Tisdale[6]

Recommendation 6a. For children with SCD who have an indication for allogeneic HSCT and an MSD, the ASH guideline panel *suggests* using myeloablative conditioning over RIC that contains melphalan/fludarabine regimens (conditional recommendation, very low certainty in the evidence about effects ⊕◯◯◯).

Recommendation 6b. For adults with SCD who have an indication for allogeneic HSCT and an MSD, the ASH guideline panel *suggests* nonmyeloablative conditioning over RIC that contains melphalan/fludarabine regimens (conditional recommendation, very low certainty in the evidence about effects ⊕◯◯◯).

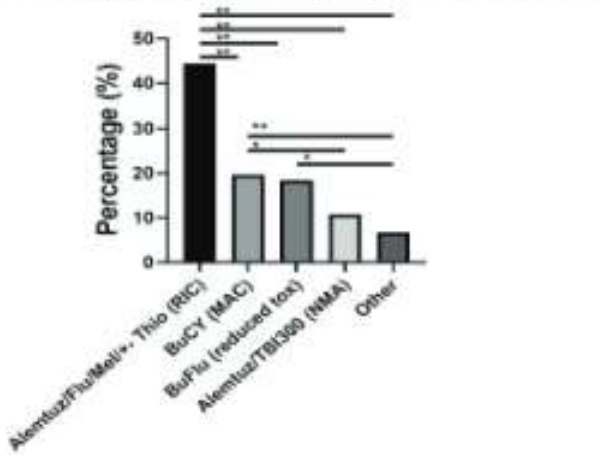
(Kanter et al, Blood 2021)

In North America, myeloablation is less commonly used

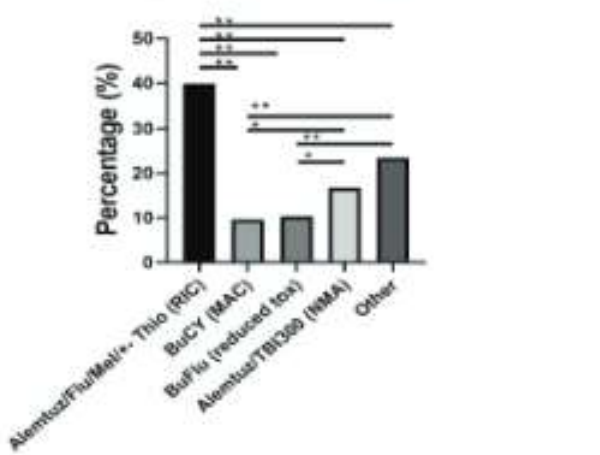
Conditioning Regimen Trends in Hematopoietic Stem Cell Transplant for Sickle Cell Disease: A Survey from the Sickle Cell Transplant Advocacy and Research Alliance (STAR) Consortium

***Alister Abraham, MD**, Center for Cancer and Immunology Research, Division of Blood and Marrow Transplantation, Children's National Hospital, Washington, DC; Elizabeth Stenger, MD, Children's Hospital of Pittsburgh, Pittsburgh; Scott Gillespie, MS, Emory University, Atlanta, GA; Emily Riehm Meier, MD, Indiana Hemophilia and Thrombosis Center, Inc., Indianapolis, IN; Gregory MT Guilcher, MD, Division of Hematology/Oncology/Transplant, Alberta Children's Hospital, Calgary, AB, Canada and John Horan, MD, MPH, Dana-Farber Cancer Institute, Boston Children's Hospital, Boston, MA*

A



B



(Abraham et al, Transplant Cell Ther 2021)

Why the difference between the ASH guidelines and North American practice?

ASH guidelines

- The highest published EFS is with myeloablative conditioning*
  - With large numbers
  - Lower rates of graft failure

Reasons to consider RIC or nonmyeloablative conditioning

- Rates of preserved fertility *might* be higher*
- Rates of GVHD are equivalent with melphalan/fludarabine and almost non-existent with the NIH regimen
- Less decline in HRQoL early post HCT

(Bernaudin et al, Blood 2007; Kanter et al, Blood 2021; Nickel et al, ASH 2021; Meacham et al, Transplant Cell Ther 2023; Kelly et al, Pediatr Blood Cancer 2012)

Adult MSD HCT for Sickle Cell Disease

The NEW ENGLAND JOURNAL of MEDICINE

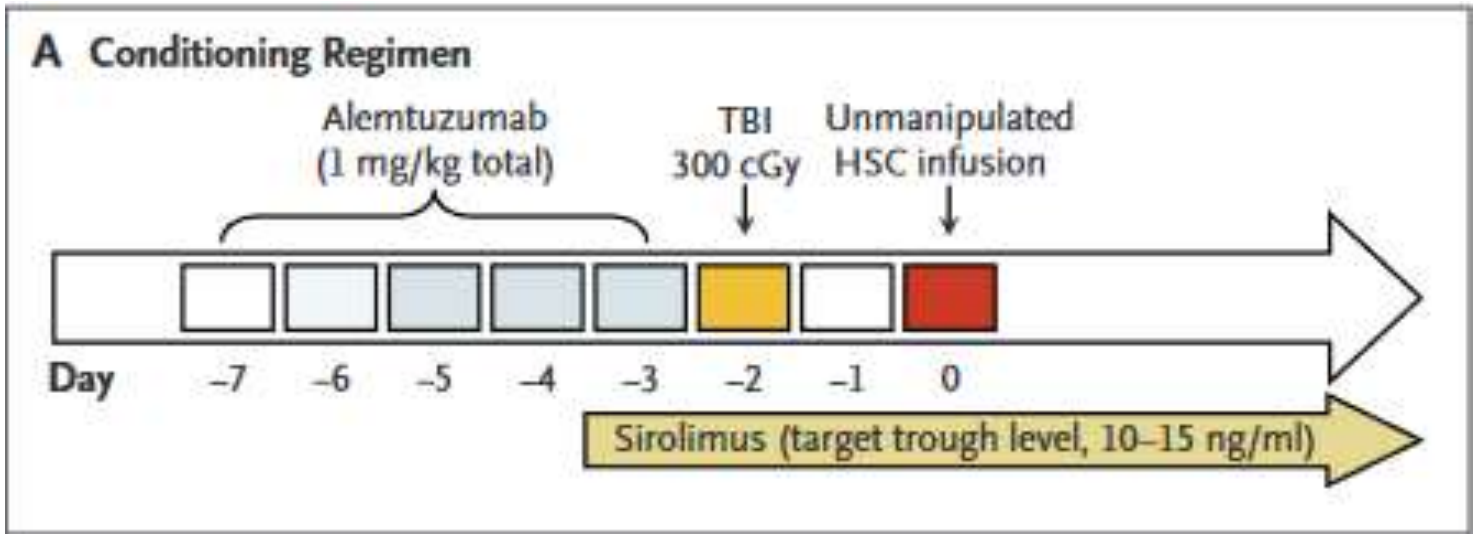
ESTABLISHED IN 1812 DECEMBER 10, 2009 VOL. 361 NO. 24

Allogeneic Hematopoietic Stem-Cell Transplantation for Sickle Cell Disease

Matthew M. Hsieh, M.D., Elizabeth M. Kang, M.D., Courtney D. Fitzhugh, M.D., M. Beth Link, R.N., Charles D. Bolan, M.D., Roger Kurlander, M.D., Richard W. Childs, M.D., Griffin P. Rodgers, M.D., Jonathan D. Powell, M.D., Ph.D., and John F. Tisdale, M.D.

(Hsieh et al, NEJM 2009)

Nonmyeloablative



(Hsieh et al, NEJM 2009)

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bjh research paper

Non-myeloablative human leukocyte antigen-matched related donor transplantation in sickle cell disease: outcomes from three independent centres

Mohsen Alzahrani,[1,†] Moussab Damlaj,[1,†] Neal Jeffries,[2] Bader Alahmari,[1] Avani Singh,[3] Damiano Rondelli,[3] John F. Tisdale,[4] Santosh L. Saraf[3,‡] and Matthew M. Hsieh[4,‡]

[1]*Division of Hematology & Hematopoietic Stem Cell Transplantation, Department of Oncology, King Abdulaziz Medical City, Riyadh, Saudi Arabia,* [2]*Office of Biostatistics Research, National Heart,*

Summary

Non-myeloablative haematopoietic progenitor cell transplantation (HPCT) from matched related donors (MRD) has been increasingly utilized in sickle cell disease (SCD). A total of 122 patients received 300 cGy of total body irradiation (TBI), alemtuzumab, unmanipulated filgrastim-mobilized peripheral blood HPC and sirolimus. The median follow-up was four years; median age at HPCT was 29 years. Median neutrophil and platelet engraftment occurred on day 22 and 19 respectively; 41 patients required no platelet transfusions. Overall and sickle-free survival at one and five years were 93% and 85% respectively. Age, sex, pre-HPCT sickle complications,

(Alzahrani et al, Br J Haematol 2021)

What about the NIH protocol in children?

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

Nonmyeloablative Matched Sibling Donor Hematopoietic Cell Transplantation in Children and Adolescents with Sickle Cell Disease

Gregory M.T. Guilcher[1,*], Dania A. Monagel[2], Alberto Nettel-Aguirre[2], Tony H. Truong[1], Sunil J. Desai[3], Aisha Bruce[3], Ravi M. Shah[1], Michael T. Leaker[2], Victor A. Lewis[1]

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[3] *Section of Pediatric Immunology/Hematology/Oncology/Palliative Care, Stollery Children's Hospital, University of Alberta, Edmonton, Canada*

(Guilcher et al., Biol Blood Marrow Transplant 2019)

Calgary Results with the NIH Protocol

- 28 patients have undergone sibling donor HCT for SCD with this protocol
  - All alive
  - No GVHD
  - No sickling crises and 27/28 have donor HbS levels
  - 1/28 with donor myeloid chimerism <50%
    - Evidence of hemolysis but no sickling crises
  - All have weaned sirolimus
    - Not true for all adults
  - Fertility preservation possible

(Guilcher et al., Biol Blood Marrow Transplant 2019 with updates)

Chimerisms in Calgary Cohort

- 22 patients with at least 2 years follow-up, median 5 years

- Myeloid median 100% donor
  - Range 41-100
  - 7/22 under 95%, 1/22 under 50%

- T-cell chimerism median 72% donor
  - Range 25-92
  - 5/22 under 50%, 1/22 under 40%

(Guilcher et al, Biol Blood and Marrow Transplant 2019 with updates)

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- **A Phase II Pilot Study of Nonmyeloablative Conditioning Hematopoietic Stem Cell Transplantation in Children with Sickle Cell Disease who have a Matched Related Major ABO-Incompatible Donor**
  - PI Dr. Tony Truong
  - Alberta Children's Hospital Trial
  - ClinicalTrials.gov Identifier: NCT03214354

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DOI: 10.1002/pbc.29893

Pediatric Blood & Cancer | aspho The American Society of Pediatric Hematology/Oncology | WILEY

TRANSPLANTATION: RESEARCH ARTICLE

Neuropsychological, behavioral, and quality-of-life outcomes in children and adolescents with sickle cell disease treated with nonmyeloablative matched sibling donor hematopoietic cell transplantation: A case series

Taryn B. Fay-McClymont[1,2,3] | Dania A. Monagel[4] | Gurpreet Singh[2] | Fiona Schulte[5] | Brian L. Brooks[1,2,6,7] | William S. MacAllister[1,2] | Naddley Désiré[8] | Aleksandra Mineyko[2,6] | Marsha Vasserman[1,2] | Michael T. Leaker[2] | Tony H. Truong[2,5] | Ravi Shah[2,5] | Victor A. Lewis[2,5] | Keith Owen Yeates[7] | Gregory M. T. Guilcher[2,5]

Neuropsychological functioning was largely average across all cognitive domains, and no pre/post-HCT differences were found to be statistically significant given the small sample size. However, effect sizes revealed moderate improvements in processing speed (Cohen's $d = .72$) and verbal memory (Cohen's $d = .60$) post-HCT, and declines in measures of attention (Cohen's $d = -.54$) and fine motor speed and dexterity (Cohen's $d = -.94$). Parents endorsed better quality of life (Cohen's $d = .91$), less impact of SCD on their family, and less worry about their child's future (Cohen's $d = 1.44$).

Conclusion: Neuropsychological functioning in a sample of children and adolescents treated uniformly with NMA MSD HCT remained stable or improved in most cognitive domains, and improvements in quality of life and family functioning were observed.

(Fay-McClymont et al, Pediatr Blood Cancer 2022)

TABLE 2 Pre- and post-HCT intellectual functioning

Patient	Intellectual functioning (pre-HCT) Standard score	Intellectual functioning (post-HCT) Standard score	Change score
1	86 [WPPSI-IV]	89 [WISC-V]	+3
2	76 [WAIS-IV]	88 [WAIS-IV]	+12
3	90[a] [WISC-IV]	83 (90[a]) [WISC-IV]	0
4	106 [WISC-IV]	110 [WISC-IV]	+4
5	91[a] [WISC-IV]	92 (91[a]) [WISC-IV]	0
6	94[a] [WISC-IV]	95 (106[a]) [WISC-IV]	+12
7	94[a] [WISC-V]	96 (88[a]) [WISC-V]	−6
8	100[a] [WISC-V]	98 (91[a]) [WISC-V]	−9
9	n/a	118 [WISC-V]	n/a

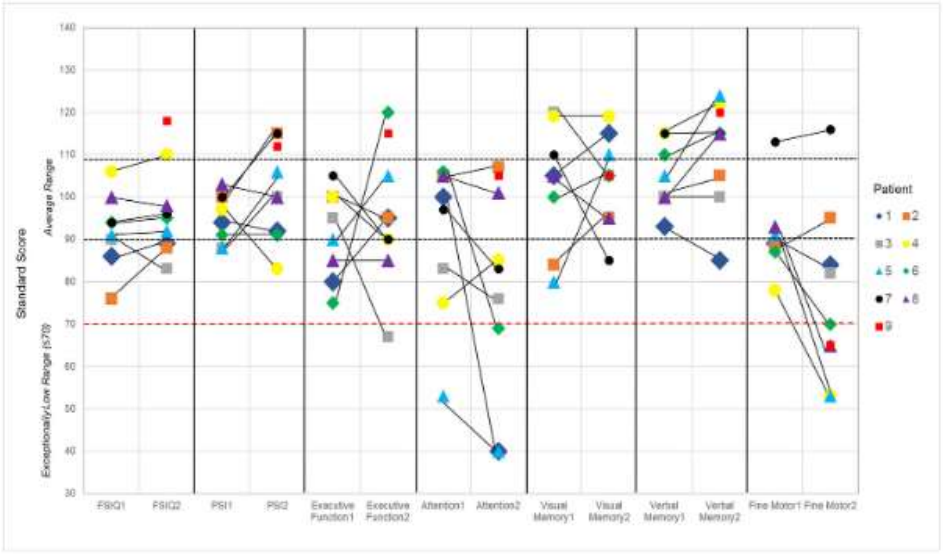

FIGURE 1 Intrapatient pre- and post-hematopoietic cell transplantation (HCT) neuropsychological functioning

(Fay-McClymont et al, Pediatr Blood Cancer 2022)

Bruce *et al.*
Health and Quality of Life Outcomes (2022) 20:118
https://doi.org/10.1186/s12955-022-02021-w

Health and Quality of Life Outcomes

RESEARCH Open Access

ADaPTS "(AD)olescents (P)ath through (T) ransplant (S)ickle cell disease"

Aisha A. K. Bruce[1,2*], Gregory M. T. Guilcher[3], Sunil Desai[1,2], Tony H. Truong[3], Michael Leaker[3], Dominic A. Alaazi[4], Sasia J. V. Pedersen[1] and Bukola Salami[4]

(Bruce et al, Health Qual Life Outcomes 2022)

I did not know what to expect. I was dreaming even that E. died. Sometimes I would dream that he died during the program. So I was always afraid until that day. Mother, Patient 1

When we started seeing the outcome…I can say our mind changed. We saw that our mind can be cooled down, compared to before the transplant…because there is no more crisis… He is doing sports.

Patient 5 added, "*I was kind of having second thoughts. Because I kind of thought that was a lot to handle.*"

Some of my family members didn't really accept me having sickle cell and stuff like that. And so like now that I don't have sickle cell, some of those family members have tried to come in contact with me and talk to me now.—Patient 2.

(Bruce et al, Health Qual Life Outcomes 2022)

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Stable renal function in children and adolescents with sickle cell disease after nonmyeloablative hematopoietic stem cell transplantation

Sasia J. V. Pedersen[1] | Dania A. Monagel[2] | Cherry Mammen[3] | Victor A. Lewis[2] | Gregory M. T. Guilcher[2] | Aisha A. Bruce[1]

[1] Department of Pediatrics, Division of Immunology, Hematology/Oncology and Palliative Care, Stollery Children's Hospital, Edmonton, AB, Canada

[2] Departments of Oncology and Pediatrics, Alberta Children's Hospital, University of Calgary, Calgary, AB, Canada

[3] Department of Pediatrics, Division of Nephrology, British Columbia Children's Hospital, Vancouver, BC, Canada

Conclusion: This study describes stable kidney function in children with SCD after NMA-HSCT without evidence of AKI or FO episodes. Rates of hyperfiltration decreased post-HSCT, which signifies that NMA-HSCT could potentially preserve long-term renal function in this population at risk of progressive chronic kidney disease. Further prospective studies are needed to confirm these novel findings.

(Pedersen et al, Pediatr Blood Cancer 2020)

ACH Endocrine Outcomes

- 17 subjects transplanted at ACH
  - Ages 3-18 y at HCT
  - 12 females
- Vitamin D deficiency
  - 4/5 with baseline testing
  - 5/5 of those tested post-HCT
- FSH
  - Baseline testing elevated in 1/5
  - 7/17 elevated post- 5 females- all values in females normalized
- 4 females with amenorrhea or oligomenorrhea had resolution
- 1 pregnancy

(Waldner et al, Pediatr Hematol Oncol 2022, photo used with permission)

DOI: 10.1002/pbc.29927

Pediatric Blood & Cancer

TRANSPLANTATION: RESEARCH ARTICLE

Pulmonary function in children and adolescents with sickle cell disease after nonmyeloablative hematopoietic cell transplantation

Dania A. Monagel[1,2] | Gregory M. T. Guilcher[3] | Alberto Nettel-Aguirre[4] | Glenda N. Bendiak[5]

A linear mixed effects model, adjusting for gender and time from HCT, suggested no significant relationship between HCT and PFT parameters, including FVC, FEV_1, and FEV_1/FVC. Interestingly, the FEF_{25-75} results exhibited a shift in the means post HCT (pre-HCT 86.2% predicted and post-HCT 93.05% predicted, *p*-value = .018).

Conclusion: Our study suggests that HCT in children with SCD may prevent the anticipated decline in pulmonary function over time.

(Monagel et al, Pediatr Blood Cancer 2022)

The SUN Clinical Trial in Children and Adolescents

721.ALLOGENEIC TRANSPLANTATION: CONDITIONING REGIMENS, ENGRAFTMENT AND ACUTE TOXICITIES | NOVEMBER 5, 2021

Nonmyeloablative HLA-Identical Sibling Donor Transplantation for Children and Young Adults with Sickle Cell Disease: Interim Results of the SUN Multicenter Phase II Trial

Robert Sheppard Nickel, KY Chiang, Steven J. Hardy, Hemalatha G Rangarajan, Sonali Chaudhury, Michael Kent, Monica Bhatia, Jeremy Zack, Vivitha Mani, Gregory M.T. Guilcher, Allistair Abraham

Blood (2021) 138 (Supplement 1): 1799.

Sickle Cell Transplant Advocacy & Research Alliance

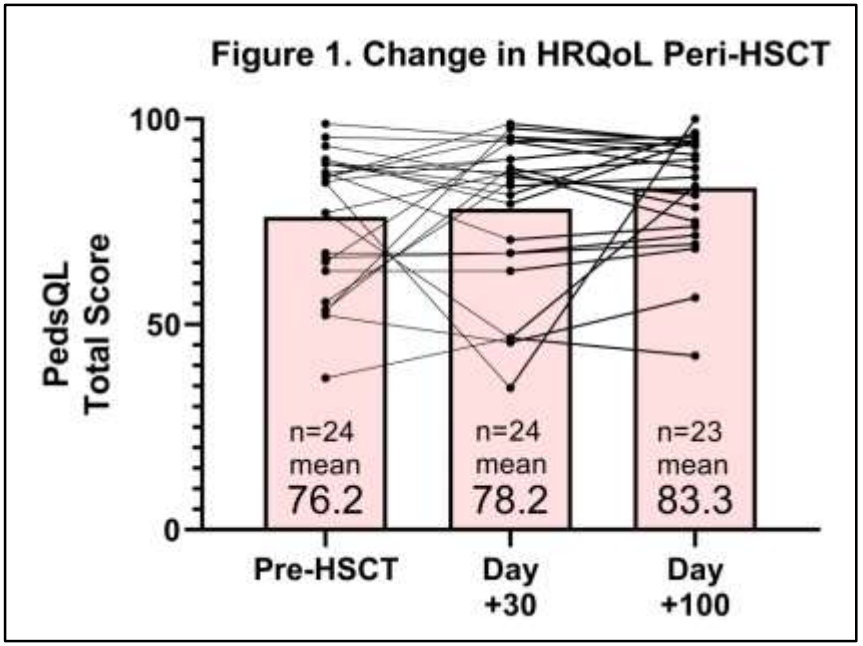
SUN Outcomes

Outcomes

- 100% survival
- 17% graft rejection

- 25% poor engraftment
  - Graft rejection
  - Stem cell boost
  - Myeloid chimerism <50%

HRQoL



(Nickel et al, ASH 2021)

SUN study changes

- Alemtuzumab to be given subcutaneous (better engraftment in Calgary cohort)
- G-CSF to be given routinely
  - Safe post-HCT
  - Better myeloid engraftment and less graft failure in Chicago
- SUNRAY study
  - Daratumumab pre-HCT for those with donor-directed red blood cell antibodies

(Shah et al, Transplant Cell Ther 2022; Saraf et al, ASH 2022)

Genotoxicity- a serious concern

Journal of *Clinical Medicine*

MDPI

Review

Clonal Hematopoiesis and the Risk of Hematologic Malignancies after Curative Therapies for Sickle Cell Disease

Lukasz P. Gondek [1], Vivien A. Sheehan [2] and Courtney D. Fitzhugh [3,*]

blood

American Society of Hematology
2021 L Street NW, Suite 900,
Washington, DC 20036
Phone: 202-776-0544 | Fax 202-776-0545
editorial@hematology.org

Increased incidence of hematologic malignancies in SCD after HCT in adults with graft failure and mixed chimerism

Tracking no: BLD-2022-017960R1

Rialnat Lawal (National Institute of Health, United States) Devdeep mukherjee (National Heart, Lung, and Blood Institute, United States) Emily Limerick (NIH/NHLBI, United States) Wynona Coles (NHLBI, United States) Matthew Hsieh (NIDDK/NHLBI, NIH, United States) Laura Dillon (National Heart, Lung, and Blood Institute, United States) Christopher Hourigan (National Heart, Lung, and Blood Institute, National Institutes of Health, United States) Courtney Fitzhugh (National Heart, Lung and Blood Institute, National Institutes of Health, United States)

(Gondek et al, J Clin Med 2022; Lawal et al, Blood 2022)

Genotoxicity- what is the risk?

- Myeloid malignancy in adults
  - All cases of MDS/AML in the NIH cohort were in adults in the setting of graft failure or mixed donor chimerism
  - No cases of myeloid malignancy in the French pediatric cohort, despite 44% with mixed donor chimerism

- Low dose TBI does not appear to have higher rates of SMN in children for non-malignant diseases

  But is this true for SCD?

KEY POINTS

- **SMN risk was highest in survivors exposed to high-dose unfractionated (600-1200 cGy) or very high-dose fractionated (1440-1750 cGy) TBI.**
- **For low-dose TBI (200-450 cGy), SMN risk was comparable to chemotherapy alone, though still twofold higher than in the general population.**

(Gondek et al, J Clin Med 2022; Bernaudin et al, Haematologica 2020; Lawal et al, Blood 2022, Baker et al, Blood 2020)

Future Directions

- High rates of donor engraftment and full donor chimerism
  - ? Clonal hematopoiesis is an adult risk
  - ? Mixed donor chimerism is safe in children
- Better understanding of long-term outcomes
  - Fertility
  - Quality of Life
  - Organ function

(Bernaudin et al, Haematologica 2020; Liggett et al, J Clin Invest 2022; Ghannam et al, Blood 2020; Fitzhugh, personal communication)

300 000 children born with SCD every year

- Most eligible recipients in the world cannot access HCT due to resources
  - **3 years of chronic transfusion = HCT cost and follow-up in low income countries**
  - **80% of children in Sub Saharan Africa die by age 10**

- Collaboration with the Uganda Cancer Institute Kampala, Uganda

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Thank you to those who inspired us to change

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Thank you for listening!

Photo courtesy of Dr. Nicolas Prud'homme