Hematopoietic Stem Cell Transplant in Sickle Cell Disease- An update

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Introduction

- Hematopoietic cell transplantation (HSCT) is an accepted form of treatment for some non-malignant hematological disorders, such as aplastic anemia and beta thalassemia major while the use of HSCT in sickle cell disease (SCD) is evolving.

- Given the highly variable clinical phenotype of sickle cell disease, early intervention in the form of transplant (HSCT) versus late is always debated. However, there are a few clear indications for HSCT in SCD.

1) Allogeneic hematopoietic stem cell transplantation for sickle cell disease:the time is now -Matthew M. Hsieh et al BLOOD **2011;118(5**) 1197-1207

Indications of HSCT

Historical indications for HSCT (patients ≤ 16 y)	NIH indications for HSCT (patients ≥ 16 y)
Stroke or CNS event lasting longer than 24 hours	Irreversible end-organ damage
Abnormal brain MRI	Stroke or clinically significant CNS event
Elevated TCD	Elevated TRV ≥ 2.6 m/s
ACS with recurrent hospitalizations	Sickle-related renal insufficiency (Cr ≥ 1.5 times the upper limit of normal or biopsy proven)
Two or more VOC requiring hospitalizations for several years	Sickle hepatopathy (including iron overload)
Osteonecrosis of multiple joints	Reversible sickle complication not ameliorated by hydroxyurea
Red cell alloimmunization	Two or more VOC requiring hospitalizations for several years
Sickle cell lung disease	Any ACS while on hydroxyurea

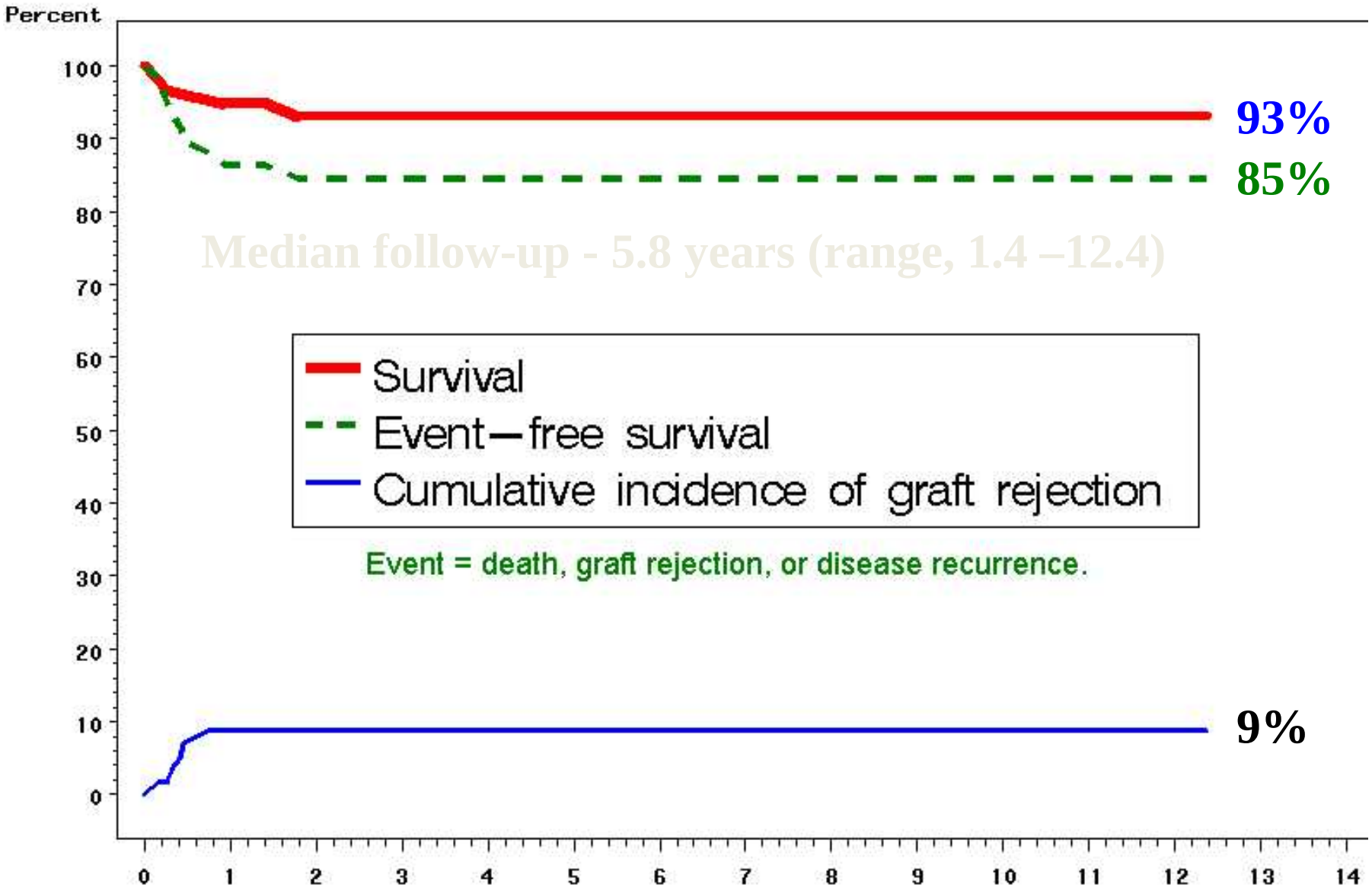
Clinical Experience With HSCT

- The first multicenter trial from USA, published in 1996, reported results in 22 patients younger than 16 years of age who received a HLA matched sibling HSCT with BuCy conditioning along with ATG.

- Kaplan Meier estimates of overall survival and event free survival at four years were 91 and 73 percent respectively (2).

2) Bone marrow transplantation for SCD Walters MC et al NEJM 1996; 335 (6)369

SCT for SCD (N=59)



Walter M, ASH/Blood 2005

- The largest published experience with HSCT consists of 87 patients with SCD who received matched sibling donor myeloablative transplants between 1988 and 2004. After a median follow up of six years-(3):

✓ Overall and event free survivals were 93 and 86 percent, respectively.

✓ Incidence of graft rejection was 2.9 percent in those who received ATG as part of their conditioning regimen and 23 percent in those who did not.

✓ TRM was 6.9 percent, with no deaths after first 12 months following HSCT.

✓ Acute GVHD of grades III-IV was seen in 20 % and chronic GVHD was present in 13 % of patients.

BLOOD 2011

- Allogeneic HSCT for sickle cell disease: the time is now.

Other approaches

- **EARLY HSCT -** in young children with SCD has been explored as a possible means of reducing SCD morbidity and HSCT associated morbidity and mortality(3).

- As compared to late transplants, early transplants were associated with-

✓ higher rate of overall survival (100 versus 88 %) and disease free survival (93 versus 80 %).

✓ A lower rate of adverse effects such as death, absence of engraftment, mixed chimerism, and relapse (7 versus 25 %).

3) HSCT for Sickle cell anemia- Vermylen C et al Bone marrow transplant 1998; 22(1);1

ALTERNATIVE DONORS

- ✓ Few patients have undergone haplo-identical and umbilical cord transplants. However, further studies are needed to determine the risk benefit ratio of this approach outside of a clinical trial.

NON-MYELOABLATIVE CONDITIONING REGIMENS

- ✓ Non-myeloablative conditioning including 300 cGy of total body irradiation plus alemtuzumab followed by prolonged administration of sirolimus post-transplant has been attempted with satisfactory results.
- ✓ 10 adults (age 16-45). At 30 mths median follow up – 100% OS, 90% EFS. NO acute or chronic gvhd.

Ref: NEJM Dec 2009 – NIH group

Conclusions

- HSCT is a potentially curative option in patients with sickle cell disease (SCD). the Current dilemma revolves around patient selection and criteria for transplant..

- In several series of patients who have undergone HSCT for SCD, five year survival rates were 90 to 97 percent, and transplant related mortality was 7 to 10 percent. SCD recurred in some patients, resulting in SCD free survival of 80 to 90 percent.

- HSCT is recommended for patients with severe symptoms of SCD that are unresponsive to treatment with transfusions and hydroxyurea if an HLA matched sibling is available as a donor.

- The use of alternative donors (eg, umbilical cord blood, mismatched related donors, or matched unrelated donors) and non – myeloablative conditioning remains uncertain in patients with SCD.

Thank you

- Dr Chirag A Shah
- Dr Arun Karanwal
- Dr Vinay Bohara
- Dr Ravish Shah
- Dr Pushkar Srivastava – Pediatric Intensivist
- Ms Upasana, Ms Dhanya, Ms Sonal and Nursing Team; Ms Khyati
- Many other members of

Apollo CBCC Cancer Care Team