Calvin Tran Genetics Recitation Week 6 -- Metabolic Pathways

Changes in the incidence, patterns and outcomes of graft failure following hematopoietic stem cell transplantation for Hurler syndrome

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Hurler syndrome

- External background information: Hurler Syndrome (HS) is a genetic metabolic disorder where the lysosomes are unable to break down large sugar molecules called glycosaminoglycans (GAG's)
    - Due to the deficiency of enzyme **alpha-L iduronidase**, which breaks down GAG's (glycosaminoglycans)
    - Result: buildup of large sugar molecules that cannot be broken down, damages multiple organ systems including nervous system, skeletal system, eyes, and heart.
    - Autosomal recessive, as opposed to Hunter syndrome which is similar but X-linked.
- Standard of care = hematopoietic stem cell transplantation (HSCT) "*the only therapy that can arrest disease progression*"
    - Donor-derived hematopoietic cells are able to secrete functional α-L-iduronidase
    - Using recombinant enzymes is a useful consideration, but the current ones available cannot cross the blood-brain barrier so are limited in application.
- Study = all Hurler Syndrome syndrome at Royal Manchester Children's Hospital or the University of Minnesota Children's Hospital from 1983 to 2016 (14 years)
    - Total 240 children, 131 pre-2004 and 109 post-2004
    - This distinction was made as grafts in the "current" era were significantly more successful (89% survival vs 58% survival)
- Analysis of HSCT technique as it is the most common treatment option.

- Historically, high rates of graft failure and transplant-related mortality.
    - Early reports:
        - 5 year survival: up to 80%, as low as 50%
        - 10 year survival: up to 80%, as low as 30%
    - Improved rates in the last ten years --- in Europe a smaller study of 62 children estimates 3-year survival of between 90-95%
    - **Purpose**: *"Graft failure remains a significant cause of treatment failure following HSCT for HS, and this is the first report specifically examining the evolution of its incidence and pattern over three decades."*

Methods

- 240 HS (Hurler Syndrome) children that first underwent HSCT (hematopoietic stem cell transplantation) at the Royal Manchester Children's Hospital or the University of Minnesota Children's Hospital.
    - Jan 1983-dec 2015
    - Confirmed HS by GAG in urine or lack of enzyme (alpha-L iduronidase)
- Obtain written/informed consent from parents, then retrieved information from transplantation databases at the hospital. (Medical files and lab records)
    - Separated patients into two groups based on transplantation date
        - Historical Era (pre-2004), 131 children
        - Current Era (post-2004), 109 children
        - Why separate? Differences in treatment, namely donor selection and GvHD prophylaxis (immunosuppression)
            - ***"Before 2002,*** *donor selection was based on donor availability from family members and registries.* ***Since 2002****, the donor hierarchy was generally as follows: (i) non-carrier HLA-matched family donor, (ii) matched unrelated cord blood, (iii) matched unrelated donor, (iv) mismatched unrelated cord blood and (v) carrier HLA-matched family donor or mismatched unrelated donor."*
            - "***Before 2005****, GvHD prophylaxis regimens were variable but consisted primarily of ev vivo T-cell depletion, CSA/methotrexate or CSA/prednisolone.* ***In 2005, GvHD prophylaxis shifted*** *almost exclusively to CSA/mycophenolate mofetil.*
- Define important endpoints related to treatment

    - OS (length of time patient survives after treatment) was defined as survival from first HSCT to last follow-up or death
    - Different categories of graft failure (4 types): primary aplastic, primary autologous reconstitution, secondary aplastic or secondary autologous reconstitution
    - Other notable endpoints (4)
        - Time to neutrophil recovery (based on a certain count)
        - Time to platelet recovery, without transfusions for 7 days (based on a certain count)
        - **Incidences of transplant-related complications**
            - Defined by the hospital already: infections
        - Degree of donor hematopoietic chimerism (symptoms of having two sets of DNA in the blood)
            - Chimerism is a **good thing**, delivers better enzyme levels and improves disease-related outcomes.
            - Recall that the procedure is a blood stem cell graft.
- Statistical Analysis
    - Chi-square where possible, Fisher's exact test instead
    - *"All variables in univariate analysis with a P-value <0.25 were included in a multivariate logistic regression* (second statistical analysis) *to assess their independent contribution to the outcome."*

Results:

Better OS (survival time) and engrafted survival rate

- *"OS has significantly improved from 60.8% (historical era) to 85.2% (current era; **P<0.001**), although follow-up is clearly shorter"*
- *"Similarly, engrafted survival has almost doubled from 41.2 to 76.3% (P<0.001)*
    - *The proportion of patients with graft failure decreased in the current era (10.1% vs 37.4%, P<0.001)*
        - Recall that graft failure doesn't mean death (can attempt a second graft)
        - All graft failures in the modern era occurred in cord blood recipients.
- *"Multivariate analysis, age was the only predictor for OS"*
- *"Deaths due to infection, GvHD and pulmonary failure have decreased significantly in the current era"*
- Identify which variables are associated with graft failure:
    - On univariate analysis, **neither pre-transplant factors (age and sex) nor transplant factors** (graft-recipient HLA disparity, total nucleated cell dose, CD34+ cell dose, graft-recipient ABO compatibility, conditioning regimen,

exposure to serotherapy, GvHD prophylaxis regimen) **correlated with graft failure in cord blood recipients** receiving busulfan-based myeloablative conditioning in the current era
    - The alternative to cord blood is a bone marrow donor
- Analysis of second transplant for graft failure
    - 60 patients failure → 48 to second transplant → 54% survival among those
        - Some died 5 years later, some died with complications arising from attempting a third transplant.
        - Deaths due to infection

Discussion

- ***The incidence of graft failure has decreased nearly three-fold*** *and* ***mortality from transplant-related causes has decreased significantly****, which may be a result of a greater availability of grafts, improved supportive care, more effective antimicrobial therapy and other factors.*
- Using this information in the future:
    - *"To improve transplant outcomes****, we must now optimize pre-transplant immune suppression in patients*** *with non-malignant diseases in the same way as we have optimized pre-transplant myelosuppression and improved the transplant outcomes of our patients."*
    - *"We have also shown that this primary or secondary aplastic-type graft failure is more commonly observed following* ***cord blood transplantation. No other transplant factors were found to be predictive of graft failure*** *within the cohort receiving cord blood."*
    - *"We have also demonstrated in this study that* ***survival rates after graft failure are good****. Almost all patients remain alive and engrafted after a* ***second transplant procedure****, including a second cord transplant. This should encourage transplant teams to be proactive in individuals with poor blood count recovery or with later aplasia* ***following a first transplant to consider expediently moving towards second transplant."***
    - ***We have highlighted the changing pattern of graft failure from insufficient myelosuppression to failure of immunosuppression.***
        - All of these are based on all modern-era deaths related to cord blood, the resulting infection-related deaths and improving outcomes since this method yields better results overall.