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HSCT for CGD? Yes, and the sooner the better.

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Abstract:

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Blood Commentary

Title: HSCT for CGD? Yes, and the sooner the better.

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Text

In this edition of Blood, Chiesa et al (on behalf of the EBMT Inborn Errors Working Party) have described excellent outcomes following allogeneic hematopoietic stem cell transplantation (HSCT) for 712 patients with chronic granulomatous disease (CGD). By some significant margin this is the largest published cohort to date [1].

As a young hematologist set on becoming a 'transplanter' I sought advice from an experienced colleague. "Know as much as you can about the underlying disease. Understand the biology and alternative therapeutic approaches. Constantly evaluate transplant outcomes. Don't just transplant because you can." 25 years later and working in transplantation for rare immunodeficiencies, this approach is essential.

CGD is an inherited multisystem primary immunodeficiency (PID) characterized by life threatening infections, immune dysregulation and granulomatous inflammation. It is caused by genetic mutations encoding proteins of the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase complex, responsible for the generation of reactive oxygen species in phagocytes. Common disease manifestations include growth failure, skin and deep-seated abscesses, fungal pneumonia, lymphadenitis, inflammatory lung disease, and colitis [2]. With genetic mutations clearly restricted to the hematopoietic system, some may consider proceeding to HSCT a 'no brainer'. Faced with a choice between potential cure or a slow decline in quality of life and reduced life expectancy, why has the decision to transplant been so fiercely debated?

CGD was first described in 1950. By the mid-1980s very few affected individuals survived into adulthood, with a median life expectancy of 10 years. Management relied on anti-microbials and careful use of corticosteroids for inflammatory complications. The earliest attempts at curative HSCT in the late 1970s and 1980s were largely unsuccessful with low rates of engraftment and unacceptably high transplant related mortality (TRM). As a result, the majority of children with CGD continued to be treated conservatively, and with steady improvements in supportive care most survived into adulthood.

Enthusiasm for HSCT was reignited in the early 2000s with the adoption of reduced toxicity conditioning regimens resulting in gradually increased numbers of CGD patients undergoing HSCT across Europe, but fewer in the US. In the last 5-10 years these transplant series have been published, demonstrating excellent outcomes with overall survival (OS) rates in excess of 80%, a reduction in infection rates and improvement in quality of life compared to pre-transplant [3-6]. Simultaneously, clinical outcomes in adulthood for non-transplanted CGD patients have become available [6, 7] identifying high rates of inflammatory complications and progressive decline in performance status, despite modern antimicrobial prophylaxis, biologics and immunosuppressants. There is good evidence that clinical outcome is closely related to residual NADPH oxidase activity [8].

The paper by Chiesa and colleagues is significant because it reports on a very large number of patients transplanted with a variety of reduced toxicity conditioning regimens in multiple centers and therefore accurately reflects contemporary outcomes following HSCT. Notably, 87% of transplants were performed *after* 2006, the era in which effective antimicrobial and antifungal prophylaxis has been available for conservatively managed patients. Their cohort included 635 children and 77 adults (>18 years at transplant), with a median age at transplant of 7 years (range, 0.1-48.6) and a median follow-up of 45 months. Although the majority of transplants were performed in early childhood, the disease burden was high, with prior infections in 68%, chronic colitis in 24% and liver or renal impairment in 14% of evaluable patients. These were rarely 'pre-emptive' transplants. The 3-year OS was 85.7% for the whole cohort (Fig 1A). Predictably, the predominant causes of death were infection (42%) and GVHD (33%), with age (p=0.009), pre-transplant colitis (p=0.01) and donor type (p=0.02) influencing outcome on univariate analysis (Tables 2 and 3). Multivariate analysis identified age and the use of a mismatched donor as statistically significant (Table 4).

Most patients (75%) received *in vivo* T cell depletion (TCD) in the form of ATG or alemtuzumab. Donor engraftment was achieved in 88% of evaluable patients, with 12% suffering primary or secondary graft failure. Of the patients who went on to have a second procedure (for both graft rejection or progressive fall in chimerism), the subsequent 3-year OS was 76.6%. As expected, overall GVHD rates were low, commensurate with TCD regimens (Fig 1G, 1H), with higher rates in the patients conditioned with Bu/Cy compared to Bu/Flu containing regimens.

For CGD patients reaching adulthood without a transplant (including those who were not offered transplant in childhood, who were symptomatic in childhood but only diagnosed as adults or those with mild disease who presented for the first time as adults) this study provides further support for the efficacy of HSCT. A number of published transplant series include adult patients [3,4,7,9], and although outcomes worsen with increasing age at transplant, OS rates of >75% are observed with a reduction in CGD-related complications.

As with other rare diseases, a timely prospective randomised controlled trial comparing HSCT with conservative therapy is not feasible, despite being highly desirable. The next best data arises from large retrospective analyses such as this.

In 2020, CGD patients have a wide array of therapeutic options available to them, including modern antibacterial and antifungal agents, prophylactic gamma interferon, minimally invasive surgery and/or interventional radiology for abscesses, monoclonal antibodies for colitis and inflammatory lung disease, HSCT and autologous gene therapy (GT). Early reports suggest GT can offer the prospect of curative therapy without the risk of GVHD, although longer term follow-up is required [10].

Just as it becomes clear that current HSCT approaches are delivering excellent results for CGD patients of all ages, conservative management improves and there remain unanswered questions. What should we recommend for patients with mild symptoms and reasonably preserved NADPH oxidase activity? Likely to do well in childhood, should these patients risk dying from a transplant in order to prevent a progressive decline in quality of life as an adult and significantly reduced life expectancy? Which patients should be considered for gene therapy?

If you are asking me? Transplant early. Inborn errors are for life, not just childhood. Adulthood with uncorrected CGD is all too often miserable.

Conflict of Interest Statement: None.

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