When the first graft fails: a strategic approach to donor selection for second transplant

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Primary graft failure (PGF) is a rare yet a significant complication after allogeneic stem cell transplantation as it is associated with high treatment-related mortality (TRM) and relapse, with very poor survival.[1] An urgent allogeneic transplant is needed to reconstitute hematopoiesis, hopefully preventing these complications.

Causes of engraftment failure include T-cell mediated rejection, donor-specific anti-HLA antibodies (DSA; B-cell mediated rejection), infections (mostly viral) and myelosuppressive drugs used pre-engraftment for treatment or prevention of infections early post-transplant. Testing for DSA prior to transplantation has become standard and patients who experience engraftment failure should be retested for DSA to make sure no rebound has occurred if low levels of DSA have been present prior to transplant.[2] Additionally, myelosuppressive medications should be avoided and viral reactivation (such as HHV6 reactivation) should be promptly treated. Notably, the use of ganciclovir for CMV reactivation early post-transplant is notorious for causing secondary graft failure. Presence of residual T-cells during the pre-engraftment period is a negative prognostic indicator and could signal impending rejection. The first step in treating patients with PGF is to increase the G-CSF dose, typically implemented by us as soon as the patient is beyond median time to engraftment.[3] A proportion of patients may recover neutrophils. However, if PGF is confirmed, the process for an urgent transplant is started, sometimes sooner than day 28 post-transplant. At this point, one of the major questions clinicians are facing is how to perform the second transplant.

Prior experience suggested that the second transplant should be performed urgently preferably with a different donor and with a lower intensity conditioning regimen with minimal toxicity that ensures reliable engraftment of donor cells.[4] The use of a different donor remains controversial, as several prior studies suggested that changing donors was not associated with better outcomes.[5,6]

In the current paper, Ma and colleagues describe their experience on the largest number of patients with graft failure analyzed to date. Most patients had primary graft failure (PGF) (71%) and most had T-cell rejection (40%), while DSA were present in approximately 21% of the patients. Median time to second transplant for PGF was 41 days, approximately two weeks from the moment the patient is diagnosed with PGF (day 28 post-transplant). Changing donor was associated with better neutrophil engraftment (92.4% *vs*. 71.4%) and platelet engraftment (76.9% *vs*. 51.8%), lower 1-year TRM (34.8% *vs*. 56.3%), and improved OS (61.9% *vs*. 42.7%), based on improved outcomes of patients with PGF, while patients with SGF did not appear to benefit. In addition, patients benefited from receiving a graft from a younger donor for the second transplant, while donor type did not impact outcomes. Conditioning with fludarabine and cyclophosphamide +/- total body irradiation was not associated with better OS compared with other regimens. Moreover, the cause of PGF did not appear to have an impact on outcomes.[7]

Most patients had a haploidentical donor for the second transplant as it would be challenging to obtain unrelated donor cells in approximately two weeks from the diagnosis of PGF.

The findings of this study have important implications for clinical practice. First, they underscore the need for a more individualized approach to second transplantations, suggesting careful consideration should be given to a different, younger donor. For patients with PGF, changing donors should be strongly considered, as it appears to offer significant benefits in terms of engraftment and survival. As the most common cause appears to be T-cell mediated rejection, the recipient's immune system likely recognized and rejected the graft, and reintroduction of same donor's cells could have a similar or even stronger immunologic rejection risk; this could potentially explain the higher engraftment rates seen in patients who switched donors.

Second, this study also highlights the importance of using younger donors for second transplants. Younger donors have been associated with better outcomes in patients receiving their first allogeneic transplant,[8-10] highlighting the fact that a strategy should be developed for donor selection for second transplants, as we begin to understand which are the factors associated with better survival for these patients.

Third, the study adds to a limited body of literature calling for the development of standardized protocols for second transplantations, which should be investigated prospectively.

In conclusion, this large multicenter study is a significant step forward in our understanding about how to perform a second allogeneic transplant for patients with graft failure. The findings provide compelling evidence that changing donors can improve engraftment rates, reduce TRM, and enhance survival in patients with PGF, and should inform clinical practice going forward. Future studies will address the questions that are at present umamswered, such as conditioning regimen for these patients, as we begin to understand not only how to select donors but also how to perform the second transplant for patients who experienced primary engraftment failure.

Disclosures

No conflicts of interest to disclose.

Contributions

PK and SC are responsible for the concept of the editorial, conducted the literature review, and wrote the manuscript. SC provided clinical insights, critical revisions and final approval of the manuscript for publication.

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