Graft failure

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‘...Try again. Fail again. Fail better...’

From *Worstward Ho!* by Samuel Beckett. (1906–1989). Irish novelist, playwright and Nobel Prize Laureate. (Fig. 1).

Graft failure (GF) following haemopoietic cell transplantation (HCT) is a relatively rare event. Valcarcel and Sureda in the 2019 EBMT manual [1] define engraftment following HCT as follows: “as the first of 3 consecutive days with an absolute neutrophil count higher than $0.5 \times 10^9/L$ sustained $>20 \times 10^9/L$ platelets and haemoglobin >80 g/L, free of transfusion requirements.” They also point out that engraftment should be confirmed by chimaerism studies. According to the authors GF occurs in $<3\text{--}5\%$ in the auto and matched allo-HCT setting but increases to 10% in the case of haplo or cord blood transplants. The thought of using one cord blood unit or two for transplantation into a 170 kg recipient should fill one with fear and trepidation. They list a number of factors that influence the risk of GF including HLA mismatches and infections.

Although retrospective studies from CIBMTR and EBMT suggest that there is no difference in GF rates between bone marrow and mobilised peripheral blood there are other major differences such as time to engraftment and Graft-versus-host disease (GvHD) especially in patients receiving HCT for severe aplastic anaemia (SAA). In terms of cell numbers, it seems that $>2.0 \times 10^6/kg$ CD34+ peripheral blood progenitors is the minimum dose required for allo HSCT when using myeloablative or reduced intensity conditioning and when using bone marrow a total nucleated cell count (TNC) of $2.0 \times 10^8/kg$ for autologous and $3.0 \times 10^8/kg$ for allo-HCT.

HCT for SAA is a different story. There is laboratory and clinical evidence that in many cases of SAA autoimmunity is an important aetiological factor. Early HCT attempts with twins (syngeneic HCT) were a failure in 50% of cases unless conditioning therapy was given before the transplant [2] and now pre-transplant cyclophosphamide is given. The use of other immunosuppressive agents including cyclosporine and anti-thymocyte globulin is effective at reducing the risk of GF [3]. The use of irradiation as part of the conditioning regimen reduces the chance of GF but is associated with the occurrence of secondary malignancies. The EBMT and CIBMTR have demonstrated an increased risk of GvHD if mobilised peripheral blood is used as the source of haematopoietic cells rather than bone marrow [4]. A second HCT after GF is not always successful [5] and whatever the disease, GF carries a poor prognosis. GF and graft rejection are not always distinguished or distinguishable and autologous recovery may occur [6] with a relatively good prognosis.

GF also occurs in vines. Unfortunately, a little terminology is required before discussing GF in wine-making. Grafting in viticulture is a technique that dates back to ancient times and means attaching the fruit-bearing part of the vine (scion) to the rootstock, which is often the part of the vine that is underground. Grafting can be done in the vineyard or in the nursery and in some cases is done mechanically. Why would you want to graft vines? As I said grafting has been used since Roman times but really came into its own during the Phylloxera crisis when grafting of resistant American rootstock into European vines saved the day [7].

Today grafting is done to take advantage of the properties of the rootstock variety. The main reason is still to graft scions onto rootstock that is resistant to diseases. In some cases, the disease is caused by nematodes (ring worms), which can transmit viruses called nepoviruses (RNA viruses in the order Picornavirales) (Fig. 2) and result in fanleaf degeneration. Apparently nepoviruses can survive for many years in nematodes and even planting disease-free vines may not have the desired result. Although a lot of research

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Fig. 1 Samuel Beckett.

Fig. 2 Nepovirus: an RNA virus causing fanleaf degeneration of vines.

has been done no rootstock is totally resistant to nepovirus and planting in a nematode-free soil is the only cure. Apart from diseases rootstock can be grafted for tolerance to soil salinity, high lime levels, water-logging or drought [8]. Reading about GF in vines brings a smile to my face. Many authors, writing in erudite journals, refer to vines having symptoms of GF. Of course, plants cannot have symptoms unless they can speak.

GF in vines cannot be compared with death of humans following HCT but is often associated with poor grape growth and severe loss of income for farmers. Hopefully with better understanding of GF in humans and vines new approaches will be discovered and GF will become a phenomenon of the past.

GF usually ends very badly for the patient despite standard measures such as recombinant hematopoietic growth factors and even a second hematopoietic cell transplant [9]. Based on experimental cellular therapies [10]), some newer cellular approaches show promise [11].

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Compliance with ethical standards

Conflict of interest The author declares that he has no conflict of interest.

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