Introduction
In 2018 disease relapse represents the most important cause of treatment failure in patients allografted for haematological malignancies. Whilst substantial advances have been made in reducing both the early and late toxicity of allogeneic stem cell transplantation (allo-SC T) there has been little or no progress in reducing the risk of relapse. At the same time treatment options for the great majority of patients who relapse remain extremely limited. Strategies with the potential to reduce the relapse risk after allo-SC T are therefore urgently required and should be informed by recent data which characterise both the risk and kinetics of disease recurrence. AML and MDS are the commonest indications for allo-SC T and serve as a valuable model for the illustration of novel strategies with the potential to reduce the risk of disease recurrence in all haematological malignancies. Broadly, such approaches may be divided into the following interventions (Figure 1):
- strategies which minimise the disease burden prior to allo-SC T
- optimisation of conditioning regimen intensity
- administration of adjunctive cellular or pharmacological therapy post-transplant with the aim of maximizing a GVL response.

Key to improving transplant outcomes will be a better understanding of the biology of disease relapse and whilst recent studies have highlighted the clonal heterogeneity of disease recurrence there remains much to be learnt concerning both the molecular and cellular basis of disease relapse.

Biology of disease relapse
The risk of disease relapse in patients allografted for AML and MDS ranges between 25-70% according to presentation karyotype and disease stage at transplant. More recently next generation sequencing has identified novel molecular predictors of disease relapse including mutations in TP53 and the RAS pathway although the precise mechanism by which these mutations contribute to post-transplant relapse remains undetermined. It has also become apparent that in patients transplanted in morphological complete remission (CR) the level of pre-transplant MRD is also an important and potentially manipulable determinant of relapse risk. Relapse rates also vary according to the intensity of the conditioning regimen deployed and are consistently observed to be higher in patients transplanted using a reduced intensity conditioning (RIC) compared with a myeloablative conditioning (MAC) regimen. Relapse rates also differ markedly between distinct RIC conditioning regimens emphasizing the importance of regimen specific comparisons of patient outcomes. Importantly the kinetics of disease relapse is not uniform and both disease and transplant specific factors determine early and late disease recurrence in patients allografted for AML.

Despite its relevance to the design of novel strategies with the capacity to decrease relapse, little is understood of the cellular biology of recurrent disease in patients allografted for AML or MDS. Whilst it is proposed that the leukemic stem/progenitor population represents the reservoir of disease relapse there have been no prospective studies addressing changes in this cellular population before and after transplantation with regard to relapse risk. Although the data is limited it appears that a significant proportion of patients allografted for AML demonstrate clonal evolution at the time of relapse- an observation of potentially major significance in the design of post-transplant strategies aimed at reducing the risk of disease relapse.

Novel transplant strategies with the potential to reduce the risk of disease relapse:

Minimising pre-transplant MRD status. The observation that pre-transplant MRD status is an important predictor of disease relapse in patients allografted for both AML and ALL in CR identifies the possibility that additional cycles of chemotherapy prior to transplant-with the aim of optimizing MRD status- may reduce the risk of post-transplant relapse. A number of retrospective registry studies have failed to demonstrate that the number of cycles of intensive chemotherapy delivered prior to either

Take Home Messages
- Pre-transplant measurable residual disease (MRD) is an important predictor of relapse risk after allogeneic stem cell transplantation (allo-SCT).
- Post-transplant pharmacological maintenance represents a potentially important novel strategy with the potential to reduce relapse risk after allo-SCT.
- Clonal evolution is present in patients relapsing after allo-SCT and this has implications for the development of post-transplant cellular or pharmacological interventions.
a MAC or RIC allograft transplant reduces relapse risk, but prospective studies of the impact of additional cycles of chemotherapy or potentially a targeted pharmacological therapy are required.

**Optimising the conditioning regimen.** The intensity of the conditioning regimen plays a key role in determining the risk of disease relapse after allo-SCT. Although most registry studies demonstrate an increased relapse risk in patients allografted using a RIC regimen the extent to which this is offset by the attendant reduction in TRM is unclear. In patients allografted for AML and MDS recent prospective studies have provided contrasting results and it remains unclear in which patients a MAC or RIC regimen is favorable. Given the pivotal role of pre-transplant MRD status and increasing evidence that relapse rates differ significantly after different RIC regimens there is an urgent need for prospective trials which compare specific RIC and MAC regimens and incorporate pre-transplant MRD assessment and meticulous co-morbidity scoring. The anti-tumor properties of both RIC and MAC regimens are impacted by both graft composition and the GVHD prophylaxis strategy adopted including the intensity of post-transplant immunosuppression and whether or not T cell depletion is utilized. Prospective studies addressing these integral components of the allograft strategy are now required in order to define both the optimal graft composition and GVHD prophylaxis regimen.

**Post-transplant strategies.** There is increasing interest in the elective administration of pharmacological or cellular therapies after allo-SCT as a strategy to reduce the risk of disease relapse. One of the most promising approaches is the prophylactic administration of donor lymphocyte infusions (DLI) to patients deemed to be at a high risk of disease relapse. A major limitation of this approach is the risk of severe GVHD associated with the administration of DLI. Currently, DLI is usually reserved for use in patients with molecular evidence of emergent disease or the presence of persistent mixed chimerism after a RIC allograft although it should be noted that there is no prospective randomised data to support the later approach.

An alternative approach incorporates elective administration of a pharmacological agent with inherent anti-tumour activity which by manipulating the kinetics of disease relapse may provide additional time for emergence of a potent GVL response. Drugs such as azacitidine (AZA), also have the potential to augment GVL by up-regulating expression of tumour antigens on residual leukemic blasts. The adjunctive administration of checkpoint inhibitors such as ipilimumab which have already been shown to have clinical activity in patients who have relapsed post-transplant is also being explored. Furthermore, effective postponement of disease relapse may serve as a strategy to defer the delivery of donor lymphocyte infusions (DLI) to a time when the risk of severe GVHD is reduced—thereby serving to dissociate GVL and GVHD.

**Future perspectives**

Important progress has been made in characterizing the determinants of disease relapse after allo-SCT. At the same time there has been significant progress in transplant technologies with the potential to reduce the risk of disease recurrence. There is therefore now a compelling requirement for enhanced registry studies through organisations such as the EBMT and CIBMTR but as importantly the accelerated delivery of prospective randomised trials, incorporating genomic analysis and sequential MRD assessment, in order to rigorously assess the broad range of therapeutic interventions with the potential to reduce the risk of disease relapse. Such collaboration between basic scientists and transplant physicians coupled with an enhanced trial delivery infrastructure offers, for the first time, the prospect of reducing relapse risk and improving transplant outcome after allogeneic transplantation.
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* Indicates papers that are highly influential or foundational in the field.