

Graft-versus-host-disease does not help acute lymphoblastic leukaemia patients with measurable residual disease

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Keywords: acute lymphoblastic leukaemia, Philadelphia chromosome, graft-versus-host-disease, measurable residual disease.

It is now well established that the curative potential of allogeneic haematopoietic stem cell transplantation (allo-HSCT) in patients suffering from acute leukaemia relies to a great extent on immune-mediated graft-versus-leukaemia (GvL) effects (Bleakley & Riddell, 2004; Dickinson *et al.*, 2017). The mechanisms of GvL effects are complex and involve many donor immune cells, including CD4+ and CD8+ T cells, NK cells and perhaps also donor B cells. Nevertheless, several observations have demonstrated a primordial role for donor T cells reacting against genetic differences between the donor and the recipient (major or minor histocompatibility antigens), with somatic mutations of the leukaemic cells leading to the generation of neoantigens – and/or aberrant expression of antigens not expressed by healthy tissues – by leukaemic cells. Unfortunately donor T cells can also target the host's healthy tissue, causing graft-versus-host disease (GvHD). While it has been clearly demonstrated that GvL effects could occur in the absence of clinical manifestations of GvHD, a number of studies have conclusively demonstrated that the occurrence of acute GvHD, chronic GvHD or both was associated with a lower incidence of leukaemia relapse (Weiden *et al.*, 1981; Baron *et al.*, 2005).

Despite the relative inefficacy of donor lymphocyte infusion (DLI) in the treatment of patients with post-transplant acute lymphoblastic leukaemia (ALL) relapses, several findings (such as a lower relapse incidence after allo-HSCT than after autologous stem cell transplantation, lower incidence of relapse in patients with GvHD, or a trend for higher risk of relapse in patients given grafts from syngeneic twins) have suggested potent GvL effects in ALL (Appelbaum, 1997; Stern *et al.*, 2014). This was confirmed by a recent report from the Center for International Blood & Marrow Transplant Research (CIBMTR), which assessed the impact of occurrence

of GvHD on allo-HSCT outcomes in a cohort of 5215 patients with ALL who had been given grafts from either a HLA-matched sibling donor, HLA-matched unrelated donor or cord blood transplantation (Yeshurun *et al.*, 2019). In that report, the authors demonstrated that both acute and chronic GvHD protected from ALL relapse. However, only a mild form of acute GvHD (grades I-II) translated to improved overall survival (OS) in patients in first or second complete remission (CR) at transplantation. In contrast, chronic GvHD occurrence was associated with better OS in the subgroup of patients with advanced ALL (Yeshurun *et al.*, 2019).

Several recent reports have highlighted the detrimental impact of persistent measurable residual disease (MRD) at transplantation on allo-HSCT outcomes in patients with ALL (Pavlu *et al.*, 2019). Since persistent MRD positivity might largely be a marker of chemo-resistant disease, one could argue that augmenting GvL effects in patients with detectable MRD at transplantation could improve the grim outcomes of these patients.

In this issue of the journal, Akahoshi *et al.* challenged this hypothesis by assessing the impact of occurrence of GvHD on allo-HSCT outcomes in a large cohort of patients with Philadelphia chromosome positive (Ph+) ALL ($n = 1022$), based on their MRD status at transplantation (Akahoshi *et al.*, 2020). To assess the impact of GvHD on transplantation outcomes, the authors used multivariate models in which occurrence of mild (grade I-II) acute, severe (grade III-IV) acute, and chronic GvHD were handled as time-dependent covariates. This has been considered the gold standard statistical tool to assess the impact of occurrence of post-transplant events on allo-HSCT outcomes (Storer, 2009). Several important observations were made by the authors.

Firstly, the authors did not observe a significantly lower risk of relapse in patients with mild acute GvHD. This was true both in patients with ($n = 231$) or without ($n = 791$) MRD positivity at transplantation. However, severe (grade III-IV) acute GvHD was associated with a lower risk of relapse in the subgroup of patients with MRD+ at transplantation. However, because of its strong association with nonrelapse mortality, this did not translate to better OS. Furthermore, severe acute GvHD was associated with significantly worse OS in patients with MRD negativity at transplantation. Indeed, there was a statistically significant interaction ($P = 0.017$) between the association of severe acute GvHD and

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OS, and MRD status at transplantation, suggesting that the occurrence of severe acute GvHD was less detrimental in patients with MRD+ at transplantation than in those without.

A second important association was that chronic GvHD prevented ALL relapse (but failed to improve OS) in the whole cohort of patients. However, interestingly, this was observed only in the subgroup of patients without MRD at transplantation (HR = 0.49, $P = 0.002$), while in the group of patients with MRD, positivity at transplantation occurrence of chronic GvHD was not associated with the risk of relapse (HR = 1.05, 95% CI 0.5–2.0).

A third important observation was that occurrence of neither mild nor severe acute GvHD improved survival from ALL relapse in patients who experienced relapse after transplantation. There was even a strong suggestion that occurrence of severe acute GvHD decreased survival from relapse. This suggests that strategies aimed at increasing GvL effects, such as discontinuation of post-grafting immunosuppression or DLI, should be done with caution even in the post-relapse setting and especially if other strategies such as administration of blinatumomab, inotuzumab ozogamicin, tyrosine kinase inhibitor or CAR T cells are possible.

There are some limitations in the study by Akahoshi *et al.*, such as the lack of data on the use of prophylactic/pre-emptive tyrosine kinase inhibitors after transplantation and the lack of standardisation of the technique for MRD assessment between the centres. Furthermore, the lack of association between GvHD occurrence and OS in the study by Akahoshi *et al.* does not necessarily mean that increasing post-grafting immunosuppression

should be done in Ph+ ALL patients. Indeed, a recent analysis of the Acute Leukaemia Working Party (ALWP) of the European Society for Blood and Marrow Transplantation (EBMT) observed that the use of anti-thymocyte globulin (ATG), although preventing grade III-IV acute GvHD as well as chronic GvHD, failed to increase OS in Ph+ ALL patients, due to a significantly higher risk of disease relapse (Giebel *et al.*, 2019).

In summary, the paper by Akahoshi *et al.* is important because it suggests that strategies aimed at favouring the occurrence of GvHD to increase GvL effects in patients with MRD+ Ph+ ALL should be avoided because occurrence of GvHD did not benefit these patients. Other approaches might focus on obtaining MRD negativity at transplantation and improving the conditioning regimen to transplantation. Finally, the role of post-transplant maintenance with blinatumomab or new-generation tyrosine kinase inhibitors in patients with Ph+ ALL should be investigated in large randomised studies.

Conflict of interest

FB has received travel grants and/or speaker honoraria from Celgene, Abbvie, Novartis, Pfizer and Sanofi. The other authors declare that they have no relevant conflict of interest.

Acknowledgements

We thank Emmanuelle Polge and Audrey Mailhol from the office of the ALWP of the EBMT. FB is Senior Research Associate at the National Fund for Scientific Research (FNRS) Belgium.

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