GvHD Prophylaxis

Effect of alemtuzumab on GvHD prevention, viral reactivation and T-cell dynamics

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Floris C. Loeff, Leiden University Medical Center, Leiden, NL, and colleagues recently published the results of a study to evaluate the effect of alemtuzumab (Camath-1H) pharmacokinetics on T-cell dynamics, graft-*versus*-host disease (GvHD) and viral reactivation in patients who received an allogeneic stem cell transplant (allo-SCT) from an alemtuzumab-based T-cell depleted graft. This prospective analysis was published in *Transplant Immunology*.

Background

GvHD is caused by donor T-cells reacting after allo-SCT (graft) and this reaction is directed against host cells. By depleting the T-cells in the graft, it is possible to reduce the incidence of GvHD, though this also minimizes the desired graft-*versus*-tumor effect. Alemtuzumab is a humanized IgG1 antibody that specifically targets CD52, a glycophosphatidylinositol-anchored protein that is expressed on lymphocytes and has been shown to decrease the incidence of severe GvHD. The effectiveness of this regimen is dependent upon CD52 expression and is relative to the amount of alemtuzumab used. Inhibition of T-cell reconstitution due to prolonged alemtuzumab exposure can increase a patient's susceptibility to infection, especially viral infections such as Epstein-Barr virus (EBV) and cytomegalovirus (CMV).

Currently there are no pharmacokinetic and pharmacodynamic data on alemtuzumab used for T-cell depleting conditioning. Therefore, this study aimed to correlate alemtuzumab levels with the degree of T-cell depletion, T-cell reconstitution and the occurrence of GvHD and viral infections in patients who received allo-SCT.

Study design and patient characteristics

- Prospective study in 36 patients treated at Leiden University Medical Center between November 2015 and February 2017
- Majority of patients had acute myeloid leukemia (n = 15) and multiple myeloma (n = 5)
- Median age at allo-SCT: 54 (26–74)
- Gender: male; 27 and female; 9

Conditioning regimen:

- Myeloablative (n = 16)
  - Cyclophosphamide with total body irradiation (n = 13) or busulfan (n = 3)
  - If unrelated donor (n = 8), administration of:

- Intravenous (IV) alemtuzumab: 15mg on days -6 and -5
- Cyclosporine from day -1 and tapered from day 30

- Non-myeloablative (n = 20)
  - IV alemtuzumab: 15mg on days -4 and -3, fludarabine and busulfan
  - If unrelated donor (n = 11): anti-thymocyte globulin (ATG): 1mg/kg on day -2
- Alemtuzumab, 20mg, was directly added “to the infusion bag” containing graft cells 30 minutes before infusion

Allo-SCT source:

- Granulocyte-colony stimulating factor (G-CSF) stimulated peripheral blood stem cell (PBSC): n = 35
- Bone marrow (BM): n = 1

Key results

In total, 28 patients received alemtuzumab (2 x 15mg IV) as part of the conditioning regimen. The authors evaluated the degree of T-cell depletion in patients, and alemtuzumab levels prior to, and following, infusions.

There was no correlation between alemtuzumab plasma levels and numbers of circulating T-cells ($P = 0.63$). However, there was a strong negative correlation between patients’ plasma volume and alemtuzumab plasma levels after infusion 1 ($P = 0.002$) and infusion 2 ($P = 0.005$) suggesting that plasma volume, not numbers of circulating lymphocytes, correlated with alemtuzumab plasma levels after alemtuzumab infusion.

The addition of alemtuzumab directly “to the bag” led to high concentrations of alemtuzumab within the grafts (estimated median 55μg/mL). The authors expected partial lysis and evaluated the number of T-cells, and alemtuzumab plasma levels in patients before, and after infusion (**Table 1**).

Table 1: Lysis of donor T-cells by alemtuzumab

	n	**Count**	**Correlation**
Absolute numbers of T-cells in transfusion bag (range)			
Median before infusion	36	14.6 x 10^9 T-cells (8.3 x 10^9 – 17.3 x 10^9 T-cells)	

Median 30 minutes after incubation	36	0.5 x 10^9 T-cells (0.2 x 10^9 –1.3 x 10^9 T-cells)	30-fold reduction (11–44 fold reduction)
Absolute numbers of circulating T-cells in peripheral blood samples (range)			
Median 30 minutes after graft infusion	30	22/30 no circulating T-cells Remaining 8 patients: 0.2 x 10^6 – 7 x 10^6 cells/L	
Alemtuzumab plasma levels in recipients (range)			
Median 30 minutes after infusion: no alemtuzumab conditioning	7	3.0μg/mL (0.4–4.5μg/mL)	No correlation with alemtuzumab levels after infusion (*P* = 0.51) Correlation between high plasma volume and low alemtuzumab plasma level (*P* = 0.43)
Before (max. 8 hours): alemtuzumab conditioning	23	2.0μg/mL (1.0–5.3μg/mL)	
Median 30 minutes after infusion: alemtuzumab conditioning	23	4.8μg/mL (2.6–10.4μg/mL)	Correlation between plasma volume and alemtuzumab plasma level before (*P* = 0.0001) and after (*P* = 0.003) infusion

The administration of 20mg of alemtuzumab directly to the graft removed the majority of circulating T-cells. The increase in levels after infusion supports the hypothesis that an excess of unbound alemtuzumab was infused into the patient.

The study investigators then looked at the impact of alemtuzumab on T-cell reconstitution.

All patients engrafted. There was no correlation between levels of T-cell reconstitution and circulating alemtuzumab. By evaluating levels of $CD52^+$ and $CD52^-$ cells, the authors showed an absence of CD4 and CD8 T-cells at week three at levels of alemtuzumab >0.7μg/mL.

The authors then looked at the rates of GvHD. Three patients were excluded due to early relapse. In total, 3 out of 33 patients developed GvHD grade II–III within 10 weeks of infusion and all three had low alemtuzumab plasma concentration (<6.5μg/mL) and high plasma volumes.

Additionally, the effect of alemtuzumab on re-activation of viral infections was studied, including EBV and CMV. Five patients were excluded from this analysis.

- EBV: 7/28 patients who were EBV-seropositive pre-transplant had reactivation of EBV, whereas no patient who was EBV-seronegative pre-transplant had reactivation.
- CMV: Of the 17 CMV-seropositive patients, all had detectable CMV reactivation within 10 weeks. Fourteen patients were treated for CMV but none of the patients developed CMV disease. All CMV-seronegative prior to transplant (n = 14) remained CMV seronegative.

Conclusion: The use of alemtuzumab as part of the conditioning regimen is effective in reducing the number of T-cells and preventing acute GvHD whilst maintaining engraftment.

High plasma concentrations of alemtuzumab prevent GvHD development in patients, after allo-SCT, who received alemtuzumab as conditioning. Patients who had alemtuzumab levels below 6.5μg/mL showed high plasma volumes. It was noted that modifying alemtuzumab doses based on plasma volume may be an option to dictate peak plasma levels.

A high persistence of alemtuzumab led to a delayed reconstitution of virus-specific T-cells and re-activation of pre-existing viral infections. However, the low incidence of infections suggests that growth of $CD52^-$ T-cells provided a protective effect against viral reactivation.

References

1. Loeff F.C. *et al.* Impact of alemtuzumab pharmacokinetics on T-cell dynamics, graft-versus-host disease and viral reactivation in patients receiving allogeneic stem cell transplantation with an alemtuzumab-based T-cell-depleted graft. Transp. Immuno. 2019 Jun 12. DOI: 10.1016/j.trim.2019.06.001