Cancer Cell International

Poster presentation

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Induction of leukemia reactive, allogeneic donor lymphocytes

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from Association for Immunotherapy of Cancer: Cancer Immunotherapy – 2nd Annual Meeting
Mainz, Germany, 6–7 May 2004

Published: 1 July 2004

Received: 28 April 2004

Cancer Cell International 2004, **4**(Suppl 1):S34

This article is available from: http://www.cancerci.com/content/4/S1/S34

The therapeutic value of donor lymphocyte infusions (DLI) in patients who relapse with AML is limited by a low efficacy and a high risk of GVHD. Therefore, we aim at generating leukemia reactive donor T cells for patients with AML. So far, 4 patient-donor pairs were evaluated (Table 1). Donor PBMC were stimulated with mature donor dendritic cells (DC), pulsed with irradiated and anti-CD34 MAb coated patient leukemic blasts (LB), or directly with cytokine (GM-CSF, IL-4, TNFalpha) treated LB. A 2–3-fold expansion of donor T cells occured in all experiments. Immunophenotyping showed a predominant outgrowth of CD4+ cells (80–95% of CD3+ cells) in all but one patient (75% CD8), with 0–1% CD56+/CD3- cells. After three weekly stimulations, donor cells were tested for IFNgamma secretion by ELISPOT assay after stimulation with irradiated leukemic blasts cells (LB) and non-leukemic controls, depending on the availability of patient cells. In 4/5 donors, cells with reactivity against patient LB with low or no reactivity against patient non-leukemic cells could be generated. In the remaining patient, the resulting donor T cell line showed a higher IFNgamma secretion after stimulation with patient PHA blasts than LB, but none after stimulation with third party LB. Direct stimulation with cytokine treated LB was performed in one donor (04), resulting in reactivity against LB and not PHA blasts, but high reactivity against 3rd party EBV-transformed B cells (LCL). In one patient so far (02), leukemia reactive donor T cells were expanded with a recently developed system using gene-modified K562 cells loaded with anti-CD3 and anti-CD28 antibodies [1,2]. One week of expansion resulted in a 10-fold increase of reactivity with sustained specificity of the resulting T cell line (not shown). Characterisation of tumor reactive donor T cells by MHC blocking experiments in one donor (02) and separate analysis of T cell subsets in a second donor (04) indicated that specific anti-leukemic reactivity was mainly mediated by CD4+ T cells in those donors.

Table 1:

	Targets				
Donors	**Leukemic blasts**	**PHA- T cell blasts**	**CD34 neg. cells**	**EBV- B cells**	**3rd party leukemic blasts**
1	252			77	21
2	11 ± 0		2 ± 1		
4	33 ± 1	4 ± 2			
7	70	113			16
10	36 ± 4	7 ± 0			

Numbers shown are spots/1e5 effector cells (IFNgamma ELISPOT) ± std err

References

1. Maus MV, *et al.*: *Nat Biotechnol* 2002, **20:**143-148.
2. Thomas AK, *et al.*: *Clin Immunol* 2002, **105:**259-72.