T cells remaining after intensive chemotherapy for acute myelogenous leukemia show a broad cytokine release profile including high levels of interferon-Î³ that can be further increased by a novel protein kinase C agonist PEP005

Journal	Cancer Immunology, Immunotherapy
Status	ONLINE FIRST
Publisher	Springer Berlin / Heidelberg
ISSN	0340-7004 (Print) 1432-0851 (Online)
Subject	Medicine
Status	ONLINE FIRST
Category	Original Article
DOI	10.1007/s00262-006-0236-5
SpringerLink Date	Saturday, November 18, 2006

Elisabeth Ersvaer[1], Peter Hampson[3], Kimberley Hatfield[1], Elling Ulvestad[4], Øystein Wendelbo[1, 2], Janet M. Lord[3], Bjørn Tore Gjertsen[1] and Øystein Bruserud[1]

(1) Section for Hematology, Institute of Medicine, The University of Bergen and Haukeland University Hospital, 5021 Bergen, Norway

(2) Division for Infectious Diseases, The University of Bergen and Haukeland University Hospital, Bergen, Norway

(3) MRC Centre for Immune Regulation, The University of Birmingham, Birmingham, UK

(4) Department of Microbiology and Immunology and The Gade Institute, Haukeland University Hospital and The University of Bergen, Bergen, Norway

Received: 9 August 2006 **Accepted:** 30 September 2006 **Published online:** 8 November 2006

Abstract Cytokines are released during T cell activation, including the potentially anti-leukemic interferon-γ (IFNγ), but also the hematopoietic growth factor granulocyte-macrophage colony-stimulating factor (GM-CSF) that enhance proliferation and inhibit apoptosis of acute myelogenous leukemia (AML) cells. In the present study we investigated the release of IFNγ and GM-CSF by circulating T cells in AML patients with chemotherapy-induced cytopenia. T cells were activated with anti-CD3 plus anti-CD28 in a whole-blood assay in the presence of their natural cytokine network. We examined 63 samples derived from 16 AML patients during 28 chemotherapy cycles. Activated T cells showed a broad

cytokine release profile, but IFNγ and GM-CSF levels showed a significant correlation and were generally higher than the other cytokine levels. Higher IFNγ and GM-CSF responses were associated with a low CD4:CD8 ratio, older patient age and no ongoing chemotherapy indicating potential utility of T cell activation regimes for the older AML patient. The cytokine levels could be further increased by the novel protein kinase C agonist PEP005, which also induced significant production of IL2 and TNFα which could contribute to anti-tumor effects in AML patients. We conclude that remaining T cells after intensive AML therapy show a broad cytokine release profile including high and significantly correlated levels of potentially anti-leukemic IFNγ and the AML growth factor GM-CSF. The final outcome of an AML-initiated T cell cytokine response will thus depend on the functional characteristics of the AML cells, in particular the relative expression of IFNγ and GM-CSF receptors which differs between AML patients.

Keywords Cytopenia - T lymphocytes - Chemotherapy - Cytokines