

P475 CONTROL LEUKEMIA BY INDUCING ANTI-CANCER IMMUNE REACTIVITY IN VIVO? POTENTIAL OF A DC-TRIGGERED MECHANISM

Topic: 03. Acute myeloid leukemia - Biology & Translational Research

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Background: There are virtually no treatment options for therapy-refractory or relapsed AML/MDS and high rates of relapse in successfully treated patients. The combination of the (clinically approved) immune-modulatory compounds GM-CSF+ Prostaglandine (PGE)1, the combination referred to as *KIT-M* converts myeloid blasts into dendritic cells of leukemic origin (DC_{leu}). After stimulation with DC_{leu}, antileukemic (T)cells are activated.

Aims: Kit-M treatment may be an attractive tool for immunotherapy in myeloid leukemia.

Methods: Generation of DC from leukemic whole blood (WB) samples. Mixed lymphocyte culture (MLC) followed by functional antileukemic assays.

Results: 1. *ex vivo*: Treatment of 65 leukemic WB samples with *KIT-M* does not induce blast proliferation, but triggers generation of mature DC/DC_{leu} and reduces tolerogenic DC. Kit treated WB *activates* the adaptive and innate immune system after MLC (Tcell proliferation, antitumor-supportive Tcells (TCRgd,Tb7), memory cells (Tcm,Tb7cm) and *downregulates* immunosuppressive Tcells (Treg4 and 8). Moreover *leukemia-specific* (interferon g (_g) and/or degranulating (_{deg})) adaptive (_{g-deg}T4,T8,TCRgd,Tb7,Tcm) and innate cells (_{g-deg}NK,NKb7,CIKb7) are *increased* and regulatory cells (_{g-deg}Treg4) *downregulated*. In addition, blast lysis is increased vs control. *Ex vivo* achieved blast lysis correlates *positively* with frequencies of mature DC/DC_{leu}, leukemia-specific T3,T4,T8,TCRgd,Tb7 and NK cells and *negatively* with Treg4 and 8. Blast lysis does not correlate with age, sex, ELN risktype, blast counts, or response to chemotherapy.

2. *In vivo* - rats: *Kit-M* treatment of 3 leukemically diseased (vs 3 control) rats (followed by sacrifice after treatment) leads to reduced blasts and Tregs in blood and spleen and increased DC_{leu} and memory-like Tcells.

3. *In vivo* - human: *Kit-M* therapy was offered to a 72 year old pancytopenic male as an individual salvage attempt (applied as continuous infusion), after discussion with the ethical committee, the patient's information about the experimental nature of the treatment and his written consent. The treatment was well tolerated and the patient improved clinically. Neutrophils in WBC increased from 10% to 50%, thrombocytes reached 100 G/l after 24 days. Immune monitoring showed a continuous increase of proliferating and non-naïve Tcells, NK, CIK- and NKT-, TH17 cells, B_{mem}-cells and DC in PB. The production of IFN γ producing T-, CIK and NKT-cells was demonstrated, suggesting an *in vivo* production/activation of (potentially leukemia-specific) cells. Immune stimulatory effects decreased after discontinuation of therapy. After 4 weeks of treatment, the patient was discharged in good clinical condition. Unfortunately, at two weeks from discharge, AML progressed and the patient died few days later.

Summary/Conclusion: Treatment of WB *ex vivo* with Kit-M leads to activation of adaptive and innate (leukemia-specific) immune reactive cells (and downregulated suppressive mechanisms) via a DC/DC_{leu} triggered mechanism –

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resulting in significantly improved blast lysis compared to controls (independent of patients' risk classification, MHC, age or sex). *In vivo* treatment of leukemically diseased rats or humans was well tolerated, led to an increase of platelets and granulocytes and stable (low) blast counts in PB – probably mediated by a (leukemia specifically) DC/DC_{leu} activated immune system. A dose defining clinical trial in carefully selected patients to confirm clinical safety and underscore clinical efficacy is being prepared.

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