NCU – Summative report for 2014

Report submission date: 2nd March 2015

Principal investigator: Satu Mustjoki

Project title: *The nordic CML study group: Immunological evaluation of factors related to the successful therapy discontinuation*

NCU grant received (€): 80 000

Project commencement and completion dates:
1.1.2013- project still continuing (grants received for 2013, 2014 and 2015)

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1. Briefly describe the project in a language understandable to non-scientists (max. 100 words)

The purpose of this project is to study how the immune system is able to control leukemia and prevent the expansion of leukemic cells. The study population consists of chronic myeloid leukemia patients who have achieved an excellent therapy response with current standard therapy (tyrosine kinase inhibitors, TKIs) and who are eligible for drug discontinuation. This study is related to clinical Euro-ski trial, which examines the probability to discontinue the TKI treatment without disease relapse. Both the clinical trial and immunological sub-study are ongoing in all Nordic countries and blood samples are collected from participating patients and extensive cellular and functional immunological studies are performed from fresh blood samples in order to find novel biomarkers, which could be used in the future to determine which patients are eligible for drug discontinuation.

2. Summarize the major findings of the project (max. 400 words)

The project started in late fall 2012. The participation in the immunological sub-study has been very active in different Nordic centers and over 140 patients have been included. From these patients, samples have been collected at the time of inclusion and then 1, 3 and 6 months after the drug discontinuation and in case of relapse. The basic immunophenotyping have been done from 142 patients and functional assays from 57 patients. The collection of follow-up samples will continue years 2015-2016. The immunophenotyping have been performed in the local university hospitals in each Nordic countries and Helsinki immunology laboratory have collected and stored the data in the electrical database. The samples for functional analysis have been sent to Helsinki core immunology laboratory (headed by the applicant) and T- and NK-cell functional analysis have been done from fresh samples. Spare cells have also been stored for later analysis.

Immunophenotyping analysis has demonstrated that imatinib treated patients who were able to maintain remission for 6 months had increased NK-cell counts at the time of drug discontinuation compared to patients who relapsed early. Furthermore, the phenotype of NK-cells was more cytotoxic (more CD57+ and CD16+cells and less CD62L+cells), and also their IFN-γ/TNF-α secretion was enhanced. Surprisingly, patients who relapsed more slowly (after 5 months) had similar baseline NK-cell counts, NK-cell proportion, and phenotype and function as patients, who were able to stay in remission.
The absolute number of T-cells or their function did not differ significantly between relapsing and non-relapsing patients at the time of treatment discontinuation. However, both CD4+ and CD8+ T-cells tended to be more mature in patients who stayed in remission compared to patients who relapsed early. The analysis of follow-up samples showed that in patients who stayed in remission the Th1 type cytokine (IFN-γ/TNF-α) secretion of CD8+T-cells increased at 6 months compared to baseline.
To conclude, low NK-cell numbers and poor cytokine secretion may predict early disease relapse after TKI discontinuation. However, patients who relapse later have high numbers of normally functioning NK-cells. Further research (detailed phenotypic analysis of NK- and T-cells including activating and inhibitory receptors and immune checkpoint molecules) and correlation of biomarker data with clinical parameters are ongoing to understand the ultimate determining factors of relapse.

3. Describe how the project has increased our knowledge of the prevention, cause and/or cure for cancer (max. 150 words)

Recent evidence suggests that the immune system plays a major role in cancer. Many novel immunotargeting drugs are tested in cancer patients with promising results. Similarly, our results in CML suggest that the active immune system is crucial when we aim for the curative treatment outcome. Patients who were able to stop the anti-cancer treatment and stay in remission had higher amount of NK-cells and also the function of the NK-cells was better than in patients who relapsed after therapy discontinuation. We hope that when we understand the mechanisms of cure in a proportion of patients, we are able to devise treatment strategies, which will help the rest of the patients to achieve similar results. For example in the case of CML, we believe that the drugs, which would activate the NK-cells, could enhance the probability of cure. However, further studies are still needed to prove this hypothesis.

4. Outline how Nordic cooperation has added value to this project (max. 100 words)

Chronic myeloid leukemia is quite a rare cancer (incidence 1-2 patients/100 000) and hence clinical studies cannot be performed within one Nordic country. Therefore the Nordic CML study group (NCMLSG) was established in 2004 to be able to conduct high-quality academic clinical studies within the Nordic region. The current Euro-Ski study is an excellent example of this strong Nordic collaboration: both the number of patients included in the clinical study

(>160 Nordic patients out of 650 total patients in Europe) and in the immunological sub-study (142 patients) succeeds all other countries.
This study is very unique also in the context of the whole Euro-Ski clinical study: no other substudies have recruited significant amount of patients, which further illustrates the strength of close Nordic collaboration.
Altogether 24 investigators (both clinical and basic research) from 4 different Nordic countries (Finland, Sweden, Norway and Denmark) have participated in the project.

5. Publications resulting from the NCU research grant

1) Abstract and oral presentation in ESH - iCMLf International Conference on CML - Biology and Therapy, September 26 - September 29, 2013 - Estoril, Portugal (http://www.esh.org/conference/esh-icmlf-international-conference-on-cml-biology-and-therapy/)

2) Abstract and oral presentation in 2013 ASH Annual Meeting and Exposition, December 7-10, 2013, New Orleans, USA
(https://ash.confex.com/ash/2013/webprogram/Paper60147.html)
Scored as a best abstract in CML therapy category and received an Abstract award.

Title of the abstract: Disease relapse after TKI discontinuation in CML is related both to low number and impaired function of NK-cells: Data from Euro-Ski

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3) Abstract and oral presentation in 16th Annual John Goldman Conference on Chronic Myeloid Leukemia: Biology and Therapy, September 04 - September 07, 2014 - Philadelphia, USA (http://www.esh.org/conference/esh-icmlf-16th-annual-john-goldman-conference-on-chronic-myeloid-leukemia-biology-and-therapy/)

4) Abstract and oral presentation in Scandinavian society for Immunology meeting and summer school, June 11-14, 2014 Reykjavik, Iceland

5) Abstract and oral presentation in 2014 ASH Annual Meeting and Exposition, December 6-9, 2014, San Francisco, USA.
(https://ash.confex.com/ash/2014/webprogram/Paper66989.html)

The abstract received an Abstract award.

Title of the abstract: Early Disease Relapse after Tyrosine Kinase Inhibitor Treatment Discontinuation in CML Is Related Both to Low Number and Impaired Function of NK-Cells

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Planned publications:

Manuscript related to 1st part of the study is under preparation. Submission is planned during spring, target journal Lancet Oncology or Journal of Clinical Oncology. The project will yield several publications as collection of follow-up samples allows several subprojects.