Søknadsinformasjon

Utlysning	Nordic Cancer Union Research Grant, 2014
Søknad	The nordic CML study group: Immunological evaluation of factors related to the successful therapy discontinuation
Søknadsid	154974
Innsendt av	Satu Mustjoki

Oppgave: Progress report

Tilordnet	Satu Mustjoki
Status	Arkivert
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RAPPORT

Briefly describe the project in a language understandable to non-scientists

The purpose of this project has been 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 have been ongoing in all Nordic countries and blood samples have been collected from participating patients. Extensive cellular and functional immunological studies have been 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.

Summarize the major findings of the project

The project started in late fall 2012. The participation in the immunological sub-study was very active in different Nordic centers and in total 132 patients were 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 all participating patients and functional assays from 57 patients. The collection of follow-up samples will continue until the end of 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 and plasma samples have also been stored for later analysis.

Our results indicate that NK cells have a central role in CML biology. Patients maintaining the remission for a longer period (>6 months) had significantly higher proportion of NK cells at the time of drug discontinuation compared to patients who relapsed early (<6 months). Furthermore, non-relapsing patients carried higher frequencies of recently discovered adaptive-like NK cells. In addition, NK cells from non-relapsing patients secreted TNF/IFN cytokines, which activate T cells. Accordingly, we noted that in non-relapsing patients the number of NK cells was associated with a Th1 type response of CD4+ T cells, which also may contribute to the antitumor immunity. Therefore, we hypothesize that an increased amount of adaptive-like NK cells may be capable of both directly killing the tumor cells and potentiating adaptive immune responses against leukemia, thereby maintaining remission after imatinib discontinuation.
Our results could guide the development of novel treatment strategies and support the rationale to use NK-cell modulating agents to increase the rates of treatment-free remission in CML. Due to unique, large patient cohort and thorough analysis of various immune cell subsets in this study, we believe that our results will be of significant interest to both hematologists and oncologists.
As the treatment costs with novel targeted drugs have steadily increased in oncology, these kind of biomarker analyses within clinical trials are of utmost importance to be able to find patients who benefit from the therapy, or in this case from the therapy discontinuation, and who would need alternative treatment options.

The results from this study have been presented 3 times as an oral presentation in the annual American Society of Hematology meeting (2013, 2014 and 2015) and each time it has received abstract achievement award highlighting the importance of the study.
The first paper of the results has now been submitted to the Cancer Discovery (Ilander et al and Mustjoki S. Increased numbers of adaptive CD56dim NK cells in chronic myeloid leukemia patients with prolonged molecular relapse free survival after imatinib discontinuation.)
2-3 additional manuscripts are expected to be written of the project during years 2016-2017.

Describe how the project has increased our knowledge of the prevention, cause and/or cure for cancer

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.

Outline how Nordic cooperation has added value to this project

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 (>200 Nordic patients out of 850 total patients in Europe) and in the immunological sub-study succeeded all other countries.
This study is very unique also in the context of the whole Euro-Ski clinical study: no other substudies have recruited as many 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.

List the publications resulting from the NCU research grant

Author(s), title, journal and edition	PMID (8 digits, only if possible)
Ilander M, Olsson-Stromberg U, Lahteenmaki H, Kasanen T, Koskenvesa P, Soderlund S, et al. Disease Relapse After TKI Discontinuation In CML Is Related Both To Low Number and Impaired Function Of NK-Cells:Data From Euro-SKI. Blood. 2013 Nov 15;122(21).	
Ilander MM, Olsson-Stromberg U, Lahteenmaki H, Tiina K, Koskenvesa P, Soderlund S, et al. Early Disease Relapse after Tyrosine Kinase Inhibitor Treatment Discontinuation in CML Is Related Both to Low Number and Impaired Function of NK-Cells. Blood. 2014 Dec 6;124(21).	
Ilander M, Olsson-Stromberg U, Lahteenmaki H, Kasanen T, Koskenvesa P, Soderlund S, et al. Disease Relapse After Tyrosine Kinase Inhibitor Treatment Discontinuation in Chronic Myeloid Leukaemia is Related to Both Low Number and Impaired Function of NK Cells. Scand J Immunol. 2014 Jun;79(6):467-8.	
Ilander M, Schlums H, Olsson-Stromberg U, Lahteenmaki H, Kasanen T, Koskenvesa P, et al. Mature, Adaptive-like CD56DIM NK Cells in Chronic Myeloid Leukemia Patients in Treatment Free Remission. Blood. 2015;126(23).	
Ilander et al and Mustjoki S. Increased numbers of adaptive CD56dim NK cells in chronic myeloid leukemia patients with prolonged molecular relapse free survival after imatinib discontinuation. 2016 Manuscript submitted to Cancer Discovery	

Brief overview of expenditures for last year 1 vedlegg (NCU_2015_budget report.docx)