Report NCU grant

Report submission date: March 3, 2011
Main applicant: Martin Jädersten
Project number: S-07/09
Project title: Pathogenesis and prognosis of MDS 5q- syndrome
NCU grant received (€): 50,000 (2010)
Project commencement and completion dates: Started 2009 – still ongoing.
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1. Brief description of the project, written in a language understandable to non-scientists (Maximum length: 100 words)

Myelodysplastic syndromes (MDS) with deletion on chromosome arm 5q (del[5q]) is a bone marrow malignancy with relatively favorable prognosis. Lenalidomide is a potent treatment for this subset of MDS, although its long-term safety has been questioned due to a high observed rate of transformation to acute myeloid leukemia. To determine whether lenalidomide potentially may be harmful it would be valuable with a suitable untreated group of patients for comparison. Since no such control cohort existed, we decided to set up a Nordic population-based registry for del(5q) MDS. We also set out to assess genetic changes that may predict disease progression.

2. Summarize the major findings of the project (Maximum length: 400 words)

We have initiated a population-based study of Nordic patients with del(5q) MDS diagnosed 2004-2013 (estimated n=700). We faced challenges such as local regulations for how to retrieve stored pathology samples and logistical issues where bone marrow smears, bone marrow sections, and cytogenetic specimens were sent to three different laboratories. Therefore we adopted a more rapid approach in parallel, pooling patients from the Karolinska Hospital in Stockholm and The King's College of Medicine in London (n=55). All serial samples from each patient underwent central pathology review, were stained for the tumor suppressor gene p53 (immunohistochemistry), and DNA was extracted from marrow slides to be used for deep sequencing (454/GS FLX) of TP53.

Stockholm-London cohort

TP53 mutations were found in 10 of 55 (18%) of patients with del(5q) MDS and were significantly associated with the risk of leukemic transformation. TP53 mutation was first detected in median about 2 years prior to clinical disease progression. The median mutational burden was 18% (range 1-55%). Overexpression of p53 by immunohistochemistry was associated with TP53 mutation, and was also associated with disease progression. However, patients with mutations leading to truncated p53 showed no overexpression.

TP53 mutations have to our knowledge not been reported previously in low-risk del(5q) MDS. In high-risk MDS del(5q) often occurs in the context of complex karyotype and is frequently accompanied by TP53 mutation. A likely explanation is that conventional Sanger sequencing has a detection threshold of 20-30%, while deep sequencing is able to detect clones down to 1% abundance. Thus, next-generation sequencing may allow early detection of emerging subclones with adverse genetic features during the course of the disease, and thus significantly improve risk stratification. Immunohistochemistry for p53 may have a value as a surrogate marker for TP53 mutation, although the correlation was not absolute.

Nordic cohort

All del(5q) MDS patients in the Stockholm county since 2004 have been entered into the registry. An ethical permit to expand the study nationally in Sweden is written and will be submitted this month. After ethical approval in Sweden expansion is planned to Norway and Denmark. This will constitute a unique patient material and will allow us to test the predictive value of a series of mutations continuously being discovered in MDS and related disorders. Moreover, it may give an indication if treatment with lenalidomide affects outcome.

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

We describe TP53 mutations for the first time, to our knowledge, in low-risk MDS with del(5q). TP53 mutation was associated with increased risk of disease progression. If the predictive value of early detection of TP53 mutations will validate in other patient groups, including our large population-based Nordic cohort, it is likely to affect clinical management; appropriate risk stratification and genetic monitoring during the course of the disease is crucial in order to offer optimal therapy, including transplantation, at the right time.

The large population-based Nordic cohort of patients with del(5q) MDS will be unique and will enable testing of the predictive value of a series of mutations continuously being discovered in MDS and related disorders. Moreover, it may give an indication if treatment with lenalidomide affects outcome.

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

The centers and the members of the Nordic MDS Group are invaluable for the population-based registry study. We rely on the cooperation of physicians and other staff in all participating countries. Thanks to a high quality health care system, a common care program for MDS by the Nordic MDS Group, and well kept patient registries, the Nordic countries provide excellent opportunities to perform population-based studies with high coverage and complete follow-up.

5. Publications directly related to this grant

Jadersten, M., L. Saft, A. E. Smith, A. Kulasekararaj, S. Pomplun, A. Hedlund, G. Gohring, R. Hast, B. Schlegelberger, A. Porwit, E. Hellstrom-Lindberg and G. J. Mufti. "TP53 mutations in low-risk myelodysplastic syndromes with del(5q) predict disease progression." ***J Clin Oncol.*** 2011, in press.

Jadersten M, Saft L, Pellagatti A, Göhring G, Wainscoat JS, Boultwood J, Porwit A, Schlegelberger B, Hellström-Lindberg E. Clonal heterogeneity in the 5q- syndrome: p53 expressing progenitors prevail during lenalidomide treatment and expand at disease progression. ***Haematologica***. 2009;94:1762-1766.