Abstract

Myelodysplastic syndromes (MDS) represent a group of clonal stem cell disorders characterized by ineffective hematopoiesis, peripheral cytopenia, morphological dysplasia and the risk of transformation to acute myeloid leukemia (AML). MDS belongs to one of the most common hematological diseases in patients over 60 years old. MDS incidence is still increasing. Appropriate therapy of MDS remains challenging. There is no curative approach besides peripheral stem cells transplantation, which is regretfully appropriate only for a small group of patients due to a higher median age of the MDS population. This is why the search for therapeutic alternatives remains paramount. MDS treatment was rather frustrating until the recent introduction of two new therapeutic approaches: immunomodulation therapy with lenalidomide and epigenetic or demethylating therapy with 5-azacytidine. Both new drugs have significantly higher effect than standard therapy. However, the precise mechanism of this effect remains unknown. As a result, we decided to initiate several research projects while introducing this promising treatment to our patients.

Our aim is to investigate the mechanism of both agents in relation to disease pathogenesis by examining changes of certain occurrences and factors prior to and during the course of therapy. In immunomodulating therapy we study the expression of several transcription factors important in hematopoiesis, changes in expression of specific cytokines, and other factors with a possible role in pathogenesis of MDS that could be influenced by treatment. Using gene expression profiling, we analyze changes in microRNAs before and during treatment. A separate goal is to study and confirm the central role of cereblon in lenalidomide sensitivity in patients with MDS and 5q deletion. In epigenetic therapy, the main goal is to study the potential differentiation effect of azacitidine. First we analyze clinical data from high risk MDS patients treated by azacitidine in our department and Czech Republic. We analyze expression of crucial differentiation factor for myeloid lineage PU.1. We found that significant subset of high risk MDS patients express low level of PU.1 due to DNA hypermethylation of PU.1 upstream regulatory element (URE). We also found significant relationship between levels of *PU.1* expression and response of patients to AZA treatment. Effects of azacitidine on *PU.1* expression and myeloid differentiation can be modified, enhanced by pre stimulation with the cytokines including granulocyte-colony stimulating factor (G-CSF)