Lenalidomide in Myelodysplastic syndrome with isolated del (5q) – Report of two cases with review of literature.

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Abstract:

Myelodysplastic syndrome (MDS) with isolated del (5q) is an MDS characterized by anemia with or without other cytopenias and/or thrombocytosis and in which the cytogenetic abnormality del(5q) occurs either in isolation or with one other abnormality, other than monosomy 7 or del (7q) (1, 2). Lenalidomide, an immunomodulator drug, has been reported to have dramatic therapeutic efficacy in patients with the 5q- syndrome. It is now considered the

standard drug for the treatment of transfusion dependent anemia in lower risk MDS with del(5) patients.

Keywords*: MDS, Isolated 5q deletion, Lenalidomide.*

Introduction:

Myelodysplastic syndrome (MDS) with isolated del (5q) is an MDS characterized by anemia with or without other cytopenias and/or thrombocytosis and in which the cytogenetic abnormality del(5q) occurs either in isolation or with one othercytogenetic abnormality, other than monosomy 7 or del (7q) (1, 2). This syndromeoccurs more often in female patients with a median age of 67 years. These patients present with symptoms related to anemia, which is often severe and usually macrocytic. Thrombocytosis is present in 30-50% of cases, whereas thrombocytopenia is uncommon. Bone marrow is usually hypercellular with reduced erythropoiesis increase in number of megakaryocytes.These megakaryocytes are smaller in size than normal and are of non-lobated and hypolobated forms. Majority of cases show cytogenetic abnormality involving an interstitial deletion of chromosome 5, of variable size, but with a predominance of large q31-q33 deletions (2). These cases may have more than one cytogenetic abnormality other than monosomy 7 or del(7).

MDS with low-risk disease and anemia associated with MDS, two parameters are important in treatment of choice. First, serum erythropoietin (sEPO) levels reflect the endogenous renal response to anemia and is a strong predictor of clinical response to anemia (4). Patients with lower risk MDS with a sEPO < 100 U/L have a greater than 70% chance of responding to ESA, whereas for those patients with sEPO > 500 U/L, a trial of ESA is usually not warranted because the response rate is <10%. Second, the presence of a deletion of the long arm of chromosome 5 (del5q) is associated with a high erythroid response rate to lenalidomide (5).

Lenalidomide is widely used to treat MDS with del(5q). The exact mechanism of action is unknown. Patients who showed a good response to treatment with lenalidomide may never need a blood product transfusion again. Lenalidomide has been reported to reverseanemia in many low risk MDS patients. One of the side effects of this therapy may be falling blood cell counts, and the patient may need to use supportive care initially. But approximately 50% of MDS patients with del 5q may acquire resistance to lenalidomide within two to three years inspite of the good response rate while being on treatment. Even though, Lenalidomide shows good response in MDS with del(5), approximately half of MDS patients with del(5q) acquire resistance to the drug within two to three years (5).

Case reports:

Case 1: 50 years old female presented with sudden onset of breathlessness. On examination, she was found to have hemoglobin of 5gm/dl with macrocytic picture and increased platelet counts (560 x 103/ul) on peripheral smear. Total leukocyte counts were normal. Direct combs test (DCT) and Serum B12 levels were normal. Erythropoietin levels were 450U/L. Bone marrow examination revealed erythroid hypoplasia with predominance of myeloid precursors and increased megakaryocytes. Megakaryocytes were showing dyspoiesis in form ofnon-lobation and hypolobation. There was no prominence of blasts. Cytogenetic and Fluorescent in situ hybridization (FISH) analysis were carried out on bone marrow sample. Both FISH and cytogenetic studies confirmed the presence of 5q deletion. She was then started on lenalidomide 10mg.

Case 2: Aknown case of hypertensive and diabetic 70 years old male, presented with history of tiredness, loss of appetite and significant weight loss. Laboratory investigations revealedhemoglobin of 6gm/dl with macrocytic anemia and thrombocytosis (721 x 103/dl).

Direct Combs test (DCT) was negative and serum B12 levels were normal. Erythropoietin levels were 254U/L. Bone marrow examination revealed erythroid hypoplasia with increased megakaryocytes and these megakaryocytes were showing dyspoiesis in form of non-lobation and hypolobation. Isolated 5q deletion was found on both Cytogenetic and FISH analysis. He was kept on follow-up with lenalidomide with 10mg.

Discussion:

MDS with isolated del(5q) genomic characteristics:Genomic annotation of the Commonly Deleted Region (CDR) of the 5q- syndrome highlighted several promising candidate genes mapping to the CDR, including the tumor suppressor gene SPARC, the ribosomal protein gene RPS14 and several microRNA genes. In a study published in 2007, the transcriptome of bone marrow CD34+ cells were investigated in a cohort of ten patients with the 5q- syndrome using microarray-based gene expression profiling. Several candidate genes mapping to the CDR of the 5qsyndrome showed haploinsufficiency in 5q- syndrome patients, including RPS14, encoding a component of the 40S ribosomal subunit, and CSNK1A1, encoding a serine/threonine kinase. Crucially, these two genes would be shown in subsequent studies to have an important role in the molecular pathogenesis of the 5qsyndrome. In a landmark study by Ebert et al in 2008, RPS14 was identified as a 5q- syndrome gene using a RNA mediated interference (RNAi)-based screen of each gene within the CDR. Knockdown of RPS14 to haploinsufficient levels in normal HSC resulted in a block in erythroid differentiation with relative preservation of megakaryocytic differentiation. In addition, RPS14 haploinsufficiency resulted in a block in the processing of pre-ribosomal RNA and in abrogation of 40S ribosomal subunit formation. Studies by Pellagatti et al have shown that CD34+ cells from patients with the 5q- syndrome have defective

expression of many ribosomal- and translation-related genes. The results of these studies suggest that the 5q- syndrome is a disorder of aberrant ribosome biogenesis, and the 5q- syndrome is now considered to be a ribosomopathy. A mouse model of the 5q- syndrome has been generated by Barlow et al using large-scale chromosomal engineering. Mice with haploinsufficiency of the Cd74-Nid67 interval (which is systemic to the CDR of the human 5q- syndrome and includes Rps14) recapitulated the key features of the human disease, including a macrocytic anemia and monolobulated megakaryocytes in the bone marrow. This '5q- mouse' showed defective bone marrow progenitor development and an accumulation of p53 protein with increased apoptosis was observed in the bone marrow cells, similar to that observed in animal models of DBA. The progenitor cell defect could be rescued by intercrossing the '5q- mouse' with p53- deficient mice, providing the first evidence that a p53- dependent mechanism underlies the pathophysiology of the 5q- syndrome.

Recently, a murine model for conditional, heterozygous inactivation of Rps14 in the bone marrow has been generated. Rps14 haploinsufficient mice showed significantly reduced hemoglobin and red blood cell counts with a significantly higher MCV. Bone marrow analysis confirmed an erythroid differentiation defect, with a significant increase in hypolobated megakaryocytes. Rps14 haploinsufficient mice also showed reduced protein synthesis and p53 induction in late-stage erythroblasts. Genetic inactivation of p53 rescued the erythroid phenotype: the erythroid differentiation defect was restored in Rps14-/+p53-/+ mice. This murine model shows that haploinsufficiency of Rps14 is sufficient to recapitulate the erythroid and megakaryocytic phenotype observed in the 5q- syndrome.

Lenalidomide:

Lenalidomide, immunomodulator drug, has been shown to have dramatic therapeutic efficacy in patients with the 5q- syndrome. Lenalidomide is now considered the standard drug for the treatment of transfusion dependent anemia in lower risk MDS with del(5q) patients. List et al evaluated lenalidomide treatment response in 148 MDS patients with del(5q) in a large multicentre phase II trial and showed transfusion independency and a complete cytogenetic remission was achieved in 67% and 45% of patients respectively. Two of our cases were in follow-up since last 6 months and both responded well to lenalidomide.

Lenalidomide acts by inhibiting the growth of MDS del(5q) erythroblasts but did not affect normal cells in culture. Lenalidomide has upregulate the several genes, including the tumor suppressor gene SPARC and the TGF-β family member activin A. SPARC, located at 5q32-q33 within the CDR of the 5q- syndrome, has anti-proliferative, anti-adhesive, and anti-angiogenic properties. One study demonstrated that lenalidomide inhibits two phosphatases, Cdc25C and PP2Acα, which are known as cell cycle regulator phosphatases. The genes of these phosphatases are located on chromosome 5q and are deleted in most patients with del(5q) MDS. Cdc25C and PP2Acα are co-regulators of the G2-M checkpoint in the cell cycle and thus their inhibition by lenalidomide leads to G2 arrest and apoptosis.

Lenalidomide also promotes the degradation of p53 by inhibiting auto-ubiquitination of MDM2 in del(5q) MDS. It has been suggested that lenalidomide restores normal MDM2 function in the 5q- syndrome to overcome p53 activation in response to ribosomal stress. Importantly, the presence of TP53 mutation has been shown to influence negatively the response to lenalidomide in del(5q) MDS in several studies. In the study by Jadersten et al the probability of a complete cytogenetic response to lenalidomide was significantly lower in TP53 mutated patients. Another study proved that the good hematological response is achieved in presence of

wild-type TP53, while none of the cases with mutated TP53 achieved a complete cytogenetic response.

However, lenalidomide is not effective in all MDS patients with isolated del (5). About half of the MDS patients with del(5q) acquire resistance to the drug within two to three years. Thus, there is a clinical need for novel treatments for MDS patients with del(5q). There are few potential new therapeutic agents for this group of patients include the translation enhancer including L-leucine and the p53 inhibitor cenersen are in clinical trials.

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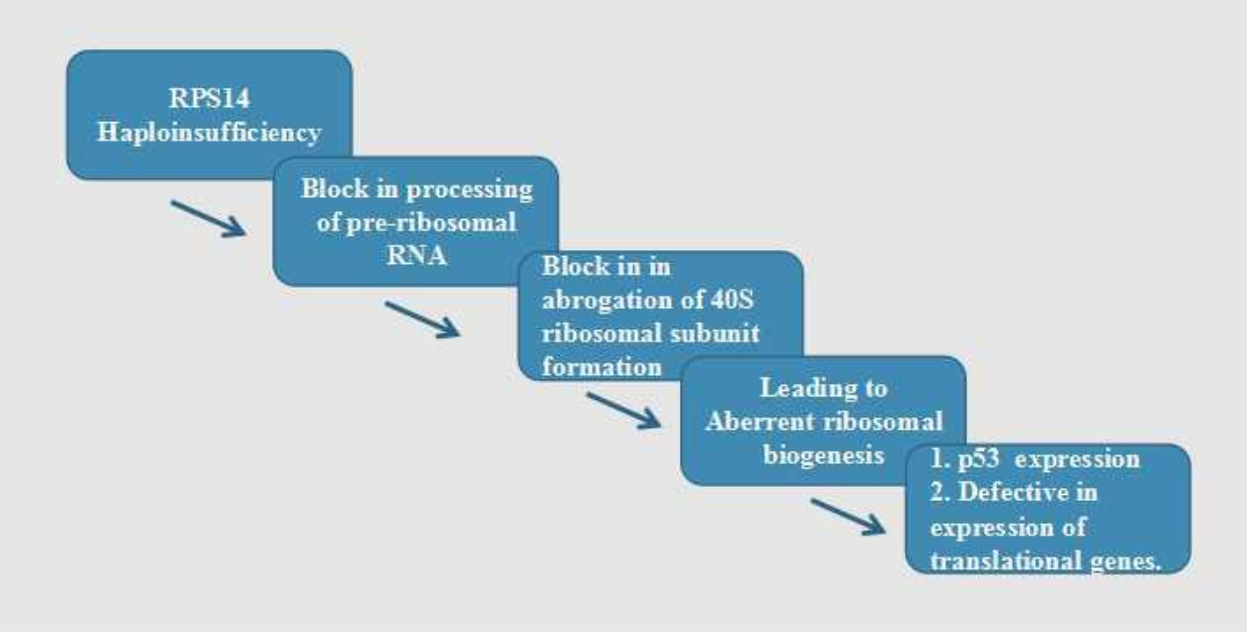
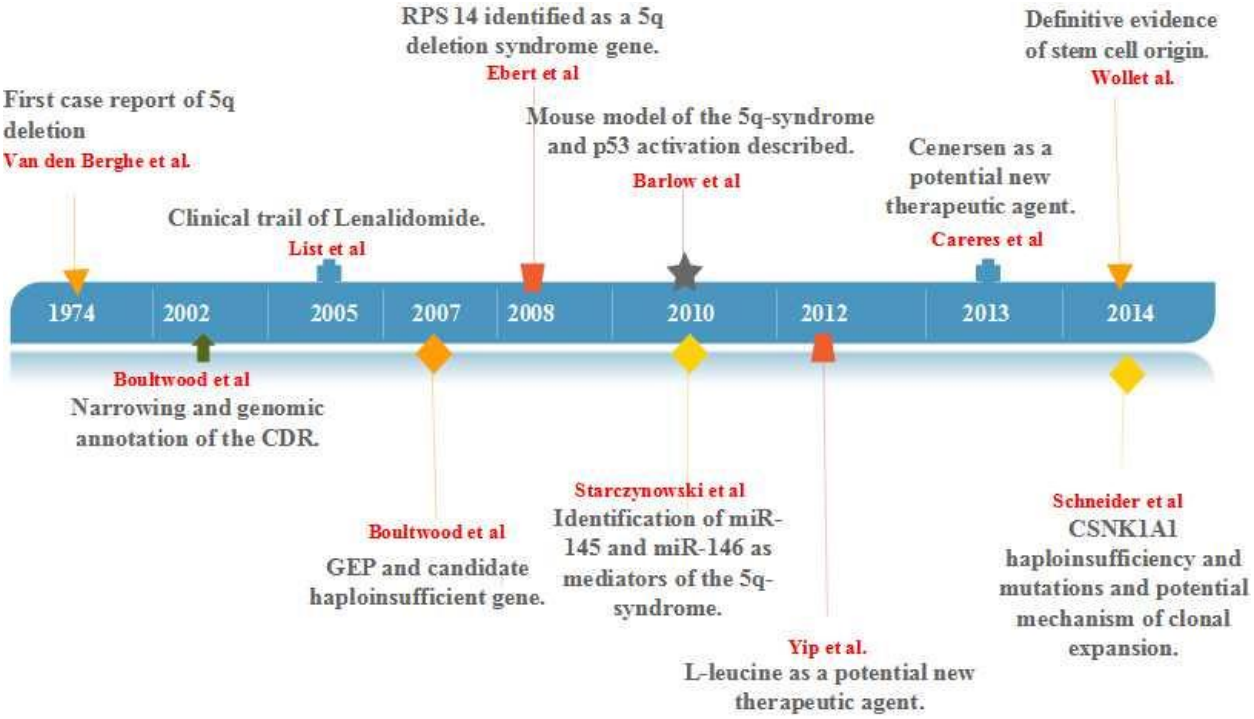


Pathogenesis of MDS with isolated del(5q)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