Leukemic Transformation in Myelodysplastic Syndrome: A Review*

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ABSTRACT

The literature was reviewed by us for leukemic transformation in the myelodysplastic syndrome (MDS). The factors reviewed included morphology, karyotype, in vitro cell culture, cellular oncogenes, genetic mutations and cell markers. Karyotypic abnormalities appeared to be most commonly associated with leukemic transformation in MDS. These abnormalities include: (1) Chromosomal abnormalities at the time of diagnosis; (2) multiple chromosomal abnormalities, especially in patients previously exposed to cytotoxic drugs, and (3) New chromosomal abnormalities following diagnosis. Leukemic transformation was also associated with non-random chromosomal abnormalities, abnormal localization of immature precursors (ALIP), dysgranulopoiesis and dysmegakaryocytopenesis, in vitro cell cultures showing high cluster/colony ratio, and N-ras oncogene mutation and activation. However, karyotypic analysis at presentation and during the course of the disease appears to be the best predictor for leukemic transformation in patients with MDS.

Introduction

Myelodysplastic syndrome (MDS) is recognized as a preleukemic condition and is characterized by pancytopenia, hypercellular marrow, and ineffective hematopoiesis. French, American and British (FAB) co-operating group has classified MDS into five categories based on morphologic criteria.6,7 The relative number of blasts in each of the categories is as follows:

1. Refractory anemia (RA): The blasts constitute less than five percent in bone marrow (BM) and less than one percent in peripheral blood (PB).
2. Refractory anemia with ringed sideroblasts (RARS): Same as RA except for ringed sideroblasts which account for more than 15 percent of nucleated cells in BM.
3. Refractory anemia with excess blasts (RAEB): Less than five percent blasts in PB and 5 to 20 percent blasts in BM.
4. Chronic myelomonocytic leukemia (CMML): Same as RAEB except for an absolute monocytosis (over $1 \times 10^9/L$) in PB.

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5. RAEB in transformation (RAEBt):
Greater than five percent blasts in PB and 20 to 30 percent blasts in BM.

When blasts exceed 30 percent in the BM, a diagnosis of acute leukemia is rendered. Leukemic transformation occurs in up to 40 percent of MDS patients. Some studies report that the development of the leukemic phase is dependent on morphological criteria. Other studies assert that transformation is predicted by karyotypic abnormalities, clonal instability, in vitro culture studies, and oncogene activation.

The many variables associated with leukemic transformation were investigated in patients with MDS. It is our belief that an understanding of the prognostic factors associated with MDS blastogenesis are important to the determination of therapeutic modalities for these patients.

Review of Literature

MORPHOLOGY

Morphologic features in MDS most associated with leukemic transformation include higher values of blasts in PB or BM, abnormalities in granulocytic or megakaryocytic series and lower ringed sideroblast proportions. Severe dyspoiesis in two or three cell lines has been associated with development of acute myeloblastic leukemia (AML). Abnormal localization of immature precursors (ALIP) involving myeloblast and promyelocyte clustering centrally rather than along the endosteum in the BM has been associated with increased leukemic transformation.

Two other patterns of transition to acute leukemia observed for patients with MDS are: (1) continuous increase in the proliferative fraction of blast cells with a corresponding decrease in the myeloid maturation index, and (2) abrupt increase in the proliferative blast cell pool and a decrease of the maturation index.

SCORING SYSTEMS

Several scoring systems have been proposed for the determination of leukemia progression. Oguma performed multivariate analysis based on presence or absence of RAEB, sex, abnormal granules in granulocytes, age and mononuclear large megakaryocytes, and divided patients into low, intermediate and high risk groups. The leukemia-free rates in low and intermediate risk groups were 95 percent and 71 percent, respectively; the high risk group had a leukemia-free rate of 10 percent at five years.

The scoring system by Varela emphasize dysmegakaryocytosis and dysgranulocytosis because of their prognostic impact on leukemia transformation.

KARYOTYPE ABNORMALITIES

Patients with MDS with abnormal karyotypes are more likely to progress to acute leukemia than those with normal karyotypes. Jacobs et al reported that the risk of leukemic transformation in patients with RA, RAEB, and RAEBt was confined to those with an abnormal karyotype.

The most common chromosomal abnormalities in MDS are monosomy 5 and 7, trisomy 8, and deletions 5q- and 7q-. Studies using clones with these abnormalities showed that they had more frequent transformation to AML. Van den Berghe reported that 5q- is associated with better survival and a low transformation rate to AML. When 5q- occurs as a part of complex karyotypic abnormalities, rapid progression to AML is observed. Cases with both 5q- and monosomy 7 have a higher frequency to progress to AML.
The risk of leukemic transformation was higher in patients in which all cells had an abnormal karyotype than those in which either all normal or some abnormal clones were present.\textsuperscript{2,29,33} Borgström reported that the presence of an aberrant clone with major karyotypic aberration or monosomy 7 indicates a higher risk of transformation to acute leukaemia.\textsuperscript{8}

Acquisition of new karyotypic anomalies during the course of MDS is reported as almost invariably associated with leukemic transformation.\textsuperscript{19} Tricot et al observed new cytogenetic anomalies in 62 percent of cases at the time of the transformation.\textsuperscript{34}

Patients with MDS who had received cytotoxic chemotherapy for malignant or non-malignant disease were apt to develop overt AML.\textsuperscript{1,14,32} Of the chemotherapeutic modalities, the alkylating agents were most implicated in this development.\textsuperscript{11} A high incidence of chromosomal abnormalities was observed in the BM cells of these patients, usually involving two or more chromosomes (i.e., complex changes).\textsuperscript{1,14,32} In addition, these patients were less likely to develop additional abnormalities during the overt leukemic phase.\textsuperscript{1,14,32}

**In vitro Cell Culture Studies**

*In vitro* cell culture studies have shown diagnostic value in predicting the evolution of MDS to acute leukemia in a number of studies.\textsuperscript{11,16} *In vitro* growth patterns are usually divided into leukemic and non-leukemic types: leukemic involving defective maturation showing a high cluster/colony ratio; non-leukemic showing persistent colony formation. Patients with MDS with leukemic growth pattern consistently had a significantly higher incidence of transformation (50 to 80 percent) than non-leukemic (21 to 40 percent).\textsuperscript{11,16} Mortensen et al also noted a correlation between increased cluster growth and rate of leukemic transformation in secondary (therapy-related) patients with MDS. Conversely, colony growth pattern was not related to leukemic progression.\textsuperscript{25}

Gold et al reported that the ratio of abnormal to normal metaphase was a predictive factor for leukemic transformation.\textsuperscript{13} This study also showed that *in vitro* granulocyte-macrophage colony formation refractoriness to inhibition by prostaglandin E correlated with AML evolution.

Greenberg et al found increased leukemic transformation in patients with low colony forming capacity in the marrow and elevated levels of colony stimulating factor in the urine.\textsuperscript{15}

Francis et al noted that the level of endogeneous colony stimulating activity was directly correlated with the rate of leukemic transformation in both primary and secondary patients with MDS.\textsuperscript{12}

**Cellular Oncogenes**

Oncogenes have been implicated in leukemic transformation in MDS.\textsuperscript{18} Hirai et al found that in patients with previously established 5q\textsuperscript{-}, activation of N-ras occurred during leukemic conversion.\textsuperscript{18} They proposed that the N-ras mutation was predictive of leukemic transformation. Other studies report that N-ras mutations may be found in early and late stages of hematopoietic malignant progression, occurring in 30 to 40 percent of both MDS and AML cases.\textsuperscript{20}

**Cell Surface Markers**

The use of antibodies directed against antigens expressed on leukemic clones during the leukemic phase has been reported.\textsuperscript{4} The My-9 antibody (a marker for immature cells of the neutrophil series) was found to bind to mature neutrophils in RAEB and RAEBt patients. This finding suggests the persistence of the antigen recognized by My-9 antibody
on the mature cells in patients at higher risk for leukemic conversion. Group H antigen expression was observed in nearly all patients with myeloid leukemia following MDS. In addition, dual expression of glycophorin A antigen, megakaryocytic antigen and myeloid antigens could be demonstrated in both MDS and "secondary" leukemia.

Discussion

The ability to predict leukemic transformation in patients with MDS offers numerous therapeutic advantages. Indeed, there is no single protocol for therapeutically addressing the patient with MDS. Perhaps the reason for this is the lack of agreement in the development of acute leukemia. Reviewing the literature, the following were concluded:

1. Patients with MDS with chromosomal abnormalities at the time of diagnosis are more likely to progress to acute leukemia.
2. Patients with MDS treated with cytotoxic drugs and possessing multiple chromosomal abnormalities are more likely to develop leukemic transformation.
3. Patients with MDS, with or without initial chromosomal abnormalities, who acquire new karyotypic changes will almost certainly progress to acute leukemia.

Among the other significant associations in MDS and the development of the leukemic phase are the non-random chromosomal abnormalities (i.e., 5q-, -5, -7, +8) which promote clonal instability and increase the likelihood of new karyotype anomalies. Some studies contend that these non-random chromosomal abnormalities may in themselves produce the leukemic phase. Cellular oncogenes and genetic mutations have been implicated in the development of leukemic phase. N-ras oncogene activation in patients with previously documented chromosomal abnormalities is particularly associated with leukemic transformation. The finding of N-ras activation in 50 percent of AML patients lends credence to this observation.

In vitro cell cultures used to identify suspected leukemic clones have been useful in predicting leukemic progression. Of the morphologic abnormalities, ALIP is the most associated with the development of the leukemic phase. Scoring systems have been developed that emphasize prognostic features (i.e., dysgranulocytopenia, dysmegakaryocytopenia) to predict progression to AML. However, despite such multivariant analyses, some authorities argue that morphology does not consistently predict leukemic progression.

Cell surface markers (i.e., My-9) offer potential use in identifying antigens expressed by leukemic clones during the leukemic phase. Group H antigen expression may be employed in a similar fashion.

It is our conclusion that karyotypic analysis at the time of diagnosis as well as during the course of disease especially following chemotherapy is the most useful tool in predicting the leukemic transformation in patients with myelodysplastic syndrome.

References


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