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Decitabine in Chronic Leukemias

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5-Aza-2′-deoxycitidine (decitabine, Dacogen™, Bloomington, MN) is a cytosine analogue that promotes hypomethylation of DNA and has documented efficacy in myeloid malignancies. Indeed, promising clinical results have been observed in acute myeloid leukemia (AML) and the myelodysplastic syndromes (MDS). Aberrant methylation has also been found in chronic leukemias, providing a rationale for investigating the use of decitabine in these diseases. There is clear evidence of molecular (hypomethylation) as well as hematologic and cytogenetic responses to decitabine in chronic myelogenous leukemia of all phases, including in patients resistant to imatinib mesylate. Clinical trials of decitabine in chronic lymphocytic leukemia are ongoing. There are many unanswered questions regarding optimizing this treatment for chronic leukemias, but successful proof-of-concept studies for hypomethylating agents move us closer to approaches that may have a significant impact on patient outcomes.
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5-Aza-2′-deoxycitidine (decitabine, Dacogen™, Bloomington, MN) is a hypomethylating cytosine analogue with efficacy in myeloid malignancies. Clinical studies of decitabine in leukemias have mostly focused on acute myeloid leukemia (AML) and the myelodysplastic syndromes (MDS) (discussed in other chapters of this issue). However, the presumed mechanism of action of decitabine—hypomethylation—does not provide it with particular selectivity in AML and MDS. In fact, methylation anomalies can be found in chronic leukemias such as chronic myelogenous leukemia (CML) and chronic lymphocytic leukemia (CLL), and there is clear evidence for decitabine activity in CML. This article will review the rationale for and clinical activity of decitabine in these chronic leukemias.

Chronic Myelogenous Leukemia

CML is one of a group of diseases referred to as myeloproliferative disorders and accounts for 15% to 20% of leukemias in adults.[16] CML is a clonal proliferation disorder that develops when a single pluripotential hematopoietic stem cell acquires a Philadelphia (Ph) chromosome, the hallmark of the disease in more than 95% of patients. Ph is characterized by a reciprocal chromosomal translocation between the long arms of chromosomes 9 and 22 where the breaks occur at positions q34 and q11 t(9;22)(q34;q11) in all hematopoietic precursors. This translocation results in the transfer of the Abelson gene (ABL) on chromosome 9 to the breakpoint cluster region gene (BCR) of chromosome 22, giving rise to the formation of two new chimeric genes. This results in a fused BCR-ABL gene on chromosome 22 and production of an abnormal tyrosine kinase protein, which affects signal transduction pathways and gene expression.[37,64] The ABL gene is the human homologue of the v-abl oncogene carried by the Abelson murine leukemia virus. This gene is ubiquitously expressed and encodes a nonreceptor tyrosine kinase. Normal ABL gene integrates signals from intracellular and extracellular sources to influence decisions in cell cycle and apoptosis. BCR protein is localized in the cytoplasm of the noncycling cell. It is suggested to play a role in cell cycle regulation since while in mitosis the BCR protein can be detected periochromosomally.[11,64]

CML leukemogenesis is a multistep phenomenon in which BCR-ABL is essential. The mechanisms that have been implicated in the malignant transformation by BCR-ABL include: (1) decreased adhesion to bone marrow stroma cells and extracellular matrix; (2) activation of mitogenic signaling; (3) inhibition of apoptosis through upregulation of several anti-apoptotic bcl-2 family members; and (4) proteosome-mediated degradation of ABL inhibitory proteins.[11] As a consequence of the disease defining translocation, the ABL-BCR fusion gene is also formed. This gene can be detected in

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upwards of 60% of CML patients. The biological and/or clinical relevance of this gene is unknown.[64]

CML has a biphasic or triphasic disease course. Patients are generally diagnosed in the chronic phase and then proceed to the blastic phase, frequently through an intermediate or accelerated phase after a median of 4 years. For chronic-phase CML patients, a variety of clinical and laboratory features previously described predict for early or late disease progression. The median survival for patients with CML is 4 to 5 years; however, the prognosis in the blastic phase is poor with a median survival of 3 to 12 months. Blastic phase is manifested by resistance to many of the currently available chemotherapies utilized for the treatment of AML, increased leukocytosis with more immature forms, and eosinophilia/basophila. In addition, various other chromosomal abnormalities are also observed such as isochromosome 17, trisomy 8, trisomy 9, an additional Ph, inversion of chromosome 16, loss of the retinoblastoma protein, or p15 silencing through promoter hypermethylation.[7,28,64]

The treatment of CML was revolutionized by the bcr-abl tyrosine kinase inhibitor imatinib mesylate (imatinib) that came forth after detailed study and understanding of the molecular pathogenesis of CML.[14] All phases of CML respond to this drug,[31,59,61] and it is now recommended for front-line therapy of this disease. However, resistance to imatinib is increasingly recognized as a clinical problem, particularly in blastic phase where it is nearly universal and in accelerated phase where it is common as well.[19,23] A number of reports have also documented the emergence of imatinib resistance in a subset of patients with chronic-phase CML, particularly those who have a poor molecular response to imatinib.[3] Resistance to imatinib can be attributed to mutations in the BCR/ABL gene in about 30% to 50% of all cases.[23,60] The prognosis of patients who develop imatinib resistance is poor.[3] Thus, there is a need for novel effective agents in CML.

Rationale for Epigenetic Therapy in CML

As our knowledge of molecular changes involved in the pathophysiology of cancer has developed, the role of epigenetic changes involving DNA methylation in gene promoters has opened up new therapeutic approaches. Epigenetic changes are essential for the maintenance of altered gene expression in malignant cells. A high degree of epigenetic changes are seen in leukemias.[58] Hypermethylation of promoter regions has been described for genes that control the growth and physiology of leukemic cells, including p15, p16, CDH13, p73, and p57. Other loci frequently abnormal in leukemias, such as MYOD1 and CALCA, may reflect general epigenetic defects in malignancies. In CML, progressive DNA methylation has been demonstrated at the translocated ABL promoter and increases in the course of CML.[11,58] The gene encoding $p15^{INK4B}$, a cyclin-dependent kinase inhibitor, is silenced by hypermethylation in 20% to 50% of CML patients.[63] CDH13 methylation has been described as a progression event in CML. Overall, there is clear evidence that progressive epigenetic defects accompany the BCR/ABL translocation that molecularly defines this disease.

Decitabine for CML

Decitabine is a pyrimidine analogue that incorporates into DNA and forms irreversible covalent bonds with DNA-methyltransferases at cytosine sites, which are targeted for methylation. This leads to DNA synthesis stalling followed by breakdown of DNA-methyltransferase; upon resumption of DNA replication without DNA-methyltransferase, one observes gene hypomethylation and reactivation of gene expression. The activation of silent genes is believed to be responsible for induction of terminal differentiation of the leukemic cells, leading to apoptosis and senescence.[45,50] At high doses, decitabine is also a cytotoxic agent. Therefore, the mechanism of decitabine activity against leukemias may be multifaceted with (1) enhanced tumor-suppressor gene expression[22,48]; (2) immune-mediated effects related to differentiation of leukemic cells into dendritic cells or changes in the cell-surface markers of malignant cells; or (3) direct cytotoxic effects on leukemic cells. An overview of clinical response to decitabine in CML is detailed in Table 1.

Decitabine in CML—Early Data

Kantarjian et al[32] evaluated the activity and toxicity of decitabine in 130 adult patients in different phases of CML; 123 were Ph-positive (64 blastic, 51 accelerated, 8 chronic) and seven had Ph-negative CML. Decitabine was administered at 100 mg/m^2 over 6 hours every 12 hours for 5 days in the first 13 patients, 75 mg/m^2 in the next 33 patients, and 50 mg/m^2 in the remaining 84 patients. Severe prolonged myelosuppression necessitated the dosage adjustments. The course was continued every 4 to 8 weeks depending on the recovery of blood counts and serial bone marrow studies. A total of 552 courses were given to the 130 patients, and patients received a median of two courses. Eighteen (28%) patients in the blastic phase achieved objective response, of whom six achieved a complete hematologic response (CHR), two achieved a partial hematologic response (PHR), seven showed hematologic improvement (HI), and three returned to second chronic phase. Five patients had cytogenetic responses. Of the patients with accelerated-phase disease, 28 (55%) achieved an objective response with 12 achieving CHRs, 10 PHRs, 3 HIs, and three returning to chronic phase. Seven of these patients had a cytogenetic response. The overall response rate for chronic-phase disease was 68% and 57% in those patients with Ph-negative CML. Median survival rates in each phase were as follows: 5 months in blastic phase, 13 months in accelerated phase, and 13 months in Ph-negative CML. There was no significant difference in response rate based on decitabine dose. A median of three courses was required to achieve both the best hematologic and cytogenetic response. The most significant adverse effect was prolonged, delayed myelosuppression, which was dose-dependent. The results from this study show that decitabine should be continued for three courses, which may indicate that de-