Optimization of Therapy for Acute Myeloid Leukemia

a report by

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Current Therapy for Acute Myeloid Leukemia

Acute myeloid leukemia (AML) is the most common form of acute leukemia in adults.1 About 60–70% of patients achieve a complete remission (CR), but only 15–25% survive five or more years, with most relapses occurring within three years. Relapse is associated with a poor response to additional therapy and shorter duration of remission.2 Five-year survival rate is 30–40% for patients <45 years and less than 10% for patients >60 years.2 Standard induction therapy consists of low dose cytosine arabinoside (ARA-C; 100–200mg/m²) administered as seven days continuous intravenous (IV) infusion plus three days of an anthracycline.3 Additional therapy after CR is required to achieve long-term disease-free survival. In patients younger than 60 years, post-remission treatment with high-dose ARA-C therapy is more effective in inducing disease-free survival than the standard dose.1 Unfortunately, AML patients classified as high-risk due to an unfavorable karyotype or secondary leukemia respond poorly to this chemotherapy.2 For these latter patients, the induction of complete remission is <50% with <10% relapse-free survival after post-remission therapy with high-dose ARA-C.1,2 There is an urgent need to improve the effectiveness of chemotherapy for these high-risk patients. For AML patients with a favorable prognosis, the major weakness of conventional chemotherapy is the maintenance of patients in CR. Even though post-remission therapy using high-dose ARA-C has increased survival of patients with AML, the optimal dose-schedule of this form of intensive chemotherapy is still unknown.1,3 About 60–70% of these latter patients will relapse after high-dose ARA-C post-remission therapy and die from disease progression. Despite the improvements in standard chemotherapy and supportive care, we need more effective chemotherapeutic agents to improve the survival of patients with AML.1

Epigenetic Therapy

Past research has shown that genetic changes, such as mutations and chromosomal aberrations and translocations, are important factors in the etiology of AML. Recent research has discovered that epigenetic changes, such as DNA methylation, can also play a key role in the development of leukemia.4 Epigenetics is defined as an inheritable change in gene expression that is not due to changes in the sequence of DNA.5 Gene silencing can occur by DNA methylation, which involves the enzymatic conversion of cytosine to 5-methylcytosine in the promoter region of genes. The normal function of this epigenetic event is to program the cell to silence the genes that are not essential for the function of each specific cell type. However, aberrant DNA methylation that silences tumor suppressor genes can also lead to the development of malignant disease.1,6 This epigenetic change can occur early in normal stem cells1 and subsequent transformation to leukemic stem cells can take place.3 An aberrant methylation pattern, such as promoter hypermethylation resulting in gene silencing, is one of the most common alterations in leukemia.4 Many loci in AML cells show aberrant DNA methylation.1,6 Since epigenetic events are reversible, they can be targets for chemotherapy intervention. An interesting epigenetic drug to use for this purpose is 5-aza-2’-deoxycytidine (decogent, decitabine, DAC). DAC is a potent inhibitor of DNA methylation, which can reactivate tumor suppressor genes silenced by DNA methylation (see Figure 1). DAC can induce in vivo differentiation and loss of clonogenicity of human leukemic cells.1,6 DAC is an S-phase specific agent with a short in vivo half-life. Like ARA-C, its pharmacological activity is dependent on the dose schedule. The first clinical studies on DAC showed that this analog could induce complete remissions with advanced acute leukemia.1,6 In May 2006, DAC was approved by the FDA for the treatment of myelodysplastic syndrome (MDS) and currently is in clinical trials for the treatment of patients with AML who fail on conventional chemotherapy. Pre-clinical studies have shown that DAC can reactivate silent p15 and other tumor suppressor genes in AML cells.1,3 Pre-clinical in vitro and in vivo studies indicate that DAC is a more potent antineoplastic agent compared with ARA-C. At equimolar concentrations, DAC produced a greater loss of clonogenicity compared with ARA-C.1,7 In a mouse model bearing L1210 leukemia at maximum tolerated doses, DAC was able to cure 100% of mice, but no cures were observed with ARA-C.1,2 These preclinical studies showed that DAC has a higher therapeutic index than ARA-C.

Optimization of DAC Dose Schedule for Acute Myeloid Leukemia Therapy

The important question is whether or not DAC will be more effective than ARA-C for the treatment of AML. Another important question is the optimal dose schedule of DAC for the treatment of patients with AML. The current recommended dose schedule of DAC for the treatment of MDS is 20mg/m²...
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Figure 1: Reactivation of Silenced Tumor Suppressor Genes by DAC

AML patients, since they respond poorly to conventional chemotherapy and have a very short life expectancy. This latter group consists of patients with adverse cytogenetics, with MDS that progressed to AML and secondary AML. In a pilot clinical trial, we administered DAC at 30mg/m²/h for 60h to patients with very advanced AML and obtained some complete remissions. However, the remissions for these patients were short, possibly due to the fact that the duration of therapy was not long enough to permit all of the leukemic cells to progress and enter the S-phase, the phase of the cell cycle in which DAC exerts its antileukemic action. For initial clinical trials, we suggest the following dose schedule: DAC at 30mg/m²/h for three days (72h). This DAC dose schedule can be modified depending on the observed response and toxicity. For example, the duration of the IV infusion can be increased by increments of 12h while maintaining the dose rate constant. The dose-limiting toxicity produced by DAC is myelosuppression.

Conclusion

In conclusion, the full therapeutic potential of epigenetic therapy of AML is unknown. DAC has a fascinating mechanism of action of reactivating silent genes that suppress leukemia progression. This action of DAC can induce the leukemic stem cells to undergo differentiation or senescence resulting in an irreversible loss of their proliferative potential. The pre-clinical studies indicate that DAC is a more potent antileukemic agent than ARA-C. These observations provide the rationale to support the initiation of clinical trials to optimize the dose schedule of DAC for patients with high-risk AML who have very little chance of survival with the current conventional chemotherapy.

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