CLINICAL UPDATE

Translating Scientific Advances into Clinical Practice

Novel Treatments in Acute Myeloid Leukemia

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H&O How common is acute myeloid leukemia (AML)?

FR AML is the most common adult acute leukemia. In 2010, approximately 12,000 people were diagnosed with AML in the United States, and approximately 9,000 died from the disease. The incidence rises with age. The majority of AML patients are older than 50–60 years. AML can arise de novo or secondary to another factor. Secondary AML may be associated with pre-existing hematologic disorders, such as myelodysplastic syndromes and myeloproliferative disorders, and prior cancer therapies, such as chemotherapy and radiotherapy.

H&O Does AML manifest differently in younger patients and older patients?

FR Younger patients tend to have a more favorable cytogenetic profile, and older patients tend to have a more unfavorable cytogenetic profile. Furthermore, in general, younger patients are able to tolerate complications associated with the use of cytotoxic chemotherapy.

H&O What treatment regimens have been used for AML?

FR For the lack of better options, the typical regimen has been a combination of 3 days of an anthracycline (idarubicin or daunorubicin) and 7 days of cytarabine. The commonly used dose of cytarabine is 100 mg/m^2 by continuous infusion daily for 7 days. A number of studies have looked at intensification of the dose of cytarabine in induction therapy. There is at least 1 meta-analysis suggesting that younger patients may benefit from intensive therapy with higher doses of cytarabine. Recent studies have also suggested that a higher dose of anthracycline may be beneficial, at least in younger patients and those with more favorable disease characteristics.

Response rates to such regimens are very dependent on age. In younger patients (<60 years), response rates as high as 70–80% can be achieved. In selected older patients, typically, the overall complete response rate is approximately 45–50%.

H&O How do patient characteristics determine treatment?

FR Patient characteristics affect the postremission strategy. Treatment options after remission include consolidation with chemotherapy or allogeneic stem cell transplant. Patients with more favorable cytogenetic characteristics are typically offered high-dose cytarabine consolidation chemotherapy courses, whereas patients with unfavorable cytogenetics are typically offered allogeneic stem cell transplant (if it is possible). For the intermediate-risk group of patients, the decision of whether or not to proceed to transplant obviously depends on the availability of a donor as well as molecular predictors of outcome.

H&O What are the opportunities for targeted therapy in AML?

FR Some of the identified molecular aberrations are targets for specific therapy. For example, in acute promyelocytic leukemia, the result of the translocation between chromosomes 15 and 17 is a fusion gene, PML-RAR-alpha, which is susceptible to the actions of all-trans retinoic acid and arsenic trioxide (Trisenox, Cephalon). In patients with FLT3-mutated AML, there are a number of tyrosine kinase inhibitors in development that may be

useful in achieving response and prolongation of relapse-free and, possibly, overall survival.

H&O What are some newer treatment options for AML?

FR The most exciting group of agents is the FLT3 inhibitors. The more potent FLT3 inhibitors include AC220 (Ambit Biosciences) and sorafenib (Nexavar, Bayer/Onyx). In a phase I study of 76 AML patients, AC220 was associated with a partial response of 18%. The overall median duration of response was 14 weeks, and the overall median survival was 14 weeks. In a phase I clinical trial of sorafenib in 15 AML patients, 73% had stable disease as the best response, although no complete responses or partial responses were observed. Either alone or in combination with chemotherapy, these agents have been effective in patients with FLT3-mutated AML.

A number of studies are looking at management of older patients with less toxic agents, including clofarabine (Clolar, Genzyme), decitabine (Dacogen, Eisai), and 5-azacytidine. Other potential agents are new formulations of older drugs, such as CPX-351 (Celator Pharmaceuticals), which is a liposomal formulation of cytarabine and daunorubicin, in a 5:1 molar ratio. Tosedostat (Cell Therapeutics) and vosaroxin (Sunesis) are other agents under investigation. Lenalidomide has been shown to be active with relatively low toxicity in patients with relapsed/refractory AML.

There have been a number of frontline studies of clofarabine, decitabine, and 5-azacytidine in older patients with AML who are not fit for chemotherapy. A randomized study of decitabine versus best supportive care in older AML patients has completed accrual, and data will be presented soon. In the relapsed setting, a randomized study of high-dose cytarabine with or without clofarabine has recently completed accrual. This study will test whether the addition of clofarabine to high-dose cytarabine improves response rates, event-free survival, and, potentially, overall survival.

Suggested Readings

American Cancer Society. What are the key statistics about acute myeloid leukemia? http://www.cancer.org/Cancer/Leukemia-AcuteMyeloidAML/DetailedGuide/leukemia-acute-myeloid-myelogenous-key-statistics.

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ClinicalTrials.gov. Decitabine maintenance in elderly acute myeloid leukemia patients. http://www.clinicaltrials.gov/ct2/show/NCT01149408?term=decitabine+aml+elderly&rank=1. Identifier: NCT01149408.

ClinicalTrials.gov. A study of clofarabine and cytarabine for older patients with relapsed or refractory acute myelogenous leukemia (AML)(CLASSIC I). http://www.clinicaltrials.gov/ct2/show/NCT00317642?term=aml+cytarabine+relapsed+clofarabine&rank=1. Identifier: NCT00317642.

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Pratz KW, Cho E, Karp J, et al. Phase I dose escalation trial of sorafenib as a single agent for adults with relapsed and refractory acute leukemias. *J Clin Oncol.* 2009;27:15s. Abstract 7065.

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