

Chemotherapy in AML

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Currently the best standard therapy for adults < 70 years of age consists of induction therapy with three daily doses of idarubicin and a seven-day continuous infusion of cytarabine. Some physicians still prefer daunorubicin or mitoxantrone instead of idarubicin, but all relevant prospective, randomized trials demonstrate one or more advantages of idarubicin over daunorubicin, and no studies demonstrate an advantage for mitoxantrone over daunorubicin. Furthermore, a meta-analysis of relevant raw data performed by Wheatley et al¹ confirmed the superiority of idarubicin over daunorubicin as an induction agent. Most studies in which daunorubicin was used during induction employed three consecutive daily doses of 45 mg/M². There is no evidence that 60 mg/M² doses, as used by some investigators², lead to a better outcome than the lower doses. The standard dose of cytarabine used in induction is 100 mg/M² daily, given as a continuous seven-day infusion. Doubling that dose³, or even increasing it by a factor of 20 or 30⁴ has resulted in little improvement, if any, in outcome of induction therapy. The addition of etoposide to the standard anthracycline + cytarabine induction regimen has improved results in some 5 but not all 6 studies.

There is general agreement that post-remission therapy is necessary to maximize disease-free and overall survival, but there is no universally accepted post-remission therapy regimen. High-dose cytarabine regimens have commonly been employed and seem to be effective, especially in younger patients with favorable cytogenetics.⁷ There is little evidence that combining other drugs

with high-dose cytarabine post-remission improves results⁸. The optimum dose of cytarabine as post-remission therapy has not been defined. It seems clear from the original study by Mayer et al⁹ that a dose of 400 mg/M² is inferior to 3 gm/M² but doses in between those have not been widely tested in an evaluable manner.

Despite the popularity of stem cell transplantation as a post-remission therapy, outcome data are disappointing for both autologous^{8,10} and allogeneic stem cell transplantation.¹⁰ In fact, Visani et al¹⁰ after an analysis of 344 papers concluded that there is no evidence that autologous stem cell transplantation is superior in terms of overall survival to chemotherapy alone, and that no overall benefit of allografting on survival was demonstrated by any trial. Also of note is the discovery that Hispanics allo-transplanted in the United States had a significantly higher risk of treatment failure (death or relapse) and overall mortality than Whites, for unknown reasons.¹¹

G-CSF¹² and GM-CSF¹³ have both been shown not to worsen disease outcome when used as supportive care in patients with AML. On the other hand, they may have the potential for inducing secondary AML or myelodysplasia in certain solid tumor patients. A doubling of the incidence of AML/MDS in 5,510 women treated with adjuvant chemotherapy for breast cancer was observed in those who received colony-stimulating factors compared with those who did not.¹⁴

Patients with AML over age 65 years generally have a poorer outcome with therapy than do

younger patients, and controversy exists as to whether older patients should be treated with regimens used in younger patients, or with less intensive therapy such as low-dose cytarabine. Kantarjian et al¹⁵ analyzed the data for 998 patients aged 65 years or more with AML or high-risk myelodysplasia treated with intensive therapy in an effort to determine prognostic factors for response and survival. The overall complete response rate was 45%. Poor prognostic factors for complete response and survival were age >75 years, unfavorable karyotype, poor performance status, longer duration of antecedent hematologic disorder and abnormal organ function. Based on these prognostic factors, they estimated that approximately 20% of the patients fell into a good prognosis group with an expected complete response rate > 60%, an induction mortality rate of 10% and a 1-year survival rate >50%. Such patients would clearly be expected to benefit from standard intensive therapy. Appelbaum et al¹⁶ studied a similar group of almost identical size. In addition to the prognostic factors noted above, they found multidrug resistance protein in 33% of AML patients < age 56 compared with 57% of patients older than 75 years. Consistent with the Kantarjian et al study¹⁵ they observed that 35% of patients younger than age 56 had unfavorable cytogenetics, compared with 51% of patients older than 75 years. It seems advisable to treat elderly AML patients with good prognostic factors as described in these two studies with standard induction chemotherapy. It is not as clear how to approach post-remission therapy. Standard high-dose cytarabine is too toxic for most elderly patients. Doses of 1.0-1.5 gm/M² have been well tolerated but not clearly effective.¹³

The best hope for improving therapy for adult AML is the development of new drugs with better activity against the disease. After a long draught, a number of recently introduced agents have already demonstrated promise. Giles et al¹⁷ studied cloretazine in patients age \geq 60 years with previously untreated AML. The drug was given alone at a dose of 600 mg/M² once, as induction therapy to 104 patients with a median age of 72 years. No patient had a favorable karyotype, and most had some significant organ dysfunction. The complete response rate was 28% and another 4% had a complete response with incomplete recovery. The one-year survival rate for the 32% of patients who were complete responders was 28%. There was minimal extramedullary toxicity in the study. The drug causes DNA crosslinks. Its active metabolite

has similarities to that of carmustine (BCNU) but it yields more than twice the DNA crosslinks, mole for mole, compared with carmustine.¹⁸ Burnett et al¹⁹ administered clofarabine (a purine nucleoside analog) 30 mg/M² daily for 5 days to 66 patients with a median age of 71 years. 62 had intermediate or poor risk cytogenetics. One course of drug was given every 28-42 days and a maximum of 3 courses were given. The CR + CRi rate was 29% and the one-year overall survival rate for responders was 32% and 28% for non-responders. Interesting, the one-year survival rate was identical for intermediate and poor cytogenetics patients. Clofarabine appears to be more toxic than cloretazine in the doses and schedules used. Serious renal toxicity developed in about 18% of patients treated with the former, and sepsis occurred in approximately 26% of those patients.

Several recent studies, if confirmed, will result in improved treatment of patients with AML in the near future. Liu et al²⁰ assessed response and survival in 60 patients with APL induced with ATRA, 25 mg/M² plus As₂O₃, 0.16 mg/kg and consolidated them with 3 cycles of daunorubicin, cytarabine and homoharringtonine, and compared results with 56 historical controls induced with ATRA alone followed by postremission chemotherapy. The experimental group also received 5 cycles of maintenance therapy with monthly ATRA, followed by As₂O₃ daily for a month, which was followed by weekly methotrexate for a month. There was no difference in CR rate between the groups, which was low (56% v 51%). However, at a median follow-up of 48 and 56 months, overall and event-free survival were significantly longer in the study group (4-year overall survival 98.1% v 83.4%, and 4-year event-free survival 94.2% v 45.6%).

The MRC²¹ studied the addition of gemtuzumab ozogamicin (GO), 3 mg/M² on day 1 of induction therapy with ADE, DA or FLAG-Ida in a randomized study of 113 patients <60 years old. CR rates were not different (85%). At 3 years, disease-free survival was significantly different in favor of those who received GO (49% v 38%). Toxicity was similar between the groups. Others²² have shown in vitro that cytotoxic activity of GO correlates with expression of protein kinase Syk and that azacytidine upregulates Syk. In another in vitro study Takahashi et al²³ demonstrated a synergistic effect of As₂O₃ and FLT 3 inhibition on cells with FLT 3-ITD.

Schlenk et al²⁴ performed a retrospective analysis of 4 German AML Study Group trials. The studies were of similar design and included 872

patients with a median age of 48 years. The results of gene analyses indicated that the 33% of patients found to be NPM1+ and FLT3 ITD – as well as those CEBPA+ had significantly higher response rates than others (88% and 83% for the former and 66% for others). Furthermore, those favorable genotypes were associated with significantly better relapse-free and overall survival. Others²⁵ have confirmed in a larger study that if not associated with FLT3-ITD mutations, mutant NPM1 appears to identify patients with improved response to treatment.

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