

# INTENSIFIED THERAPY FOR ACUTE MYELOID LEUKAEMIA

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The treatment of acute myeloid leukemia (AML) has improved over the last two decades with better supportive measures and post-induction bone marrow transplantation.<sup>(1-3)</sup> However, with standard induction regimens, approximately 30% of patients still fail to achieve a complete remission, and remission duration is often only about 12 months.<sup>(1-3)</sup> Patients fail to be cured from AML because they may be resistant to anti-leukemia drugs or they die of complications of bone marrow failure. The Australian Leukemia Study Group (ALSG) has studied strategies to improve leukemia control by changing induction treatment.

Etoposide is a semi-synthetic podophyllotoxin derivative with activity as a single agent and in combination in relapsed patients with AML.<sup>(5-9)</sup> The ALSG initially studied an intensified induction therapy with etoposide.<sup>(10)</sup> Previously untreated patients with AML aged 15 to 70 years were randomised to either cytarabine 100 mg/m<sup>2</sup>/d continuous intravenous (IV) infusion days 1 through 7, daunorubicin (DNR) 50 mg/m<sup>2</sup>/d IV days 1 through 3 (7-3), or the same drugs intensified with etoposide 75 mg/m<sup>2</sup>/d IV days 1 through 7 (7-3-7) as induction therapy. Patients achieving complete remission (CR) received two courses of consolidation therapy (5-2 or 5-2-5) followed by maintenance therapy. Of 264 eligible patients, CR occurred in 56% of 7-3 and 59% of 7-3-7 patients; 7-3-7 significantly improved remission duration (P = .01). The median remission duration was 12 months for 7-3 and 18 months for 7-3-7. Survival was similar when the two arms were compared overall. Subset analysis performed to identify patients with the most benefit showed that etoposide significantly prolonged remission duration in younger patients (less than 55 years) with a median of 12 months for 7-3 and 27 months for 7-3-7 (P = .01). Survival appeared to be prolonged with 7-3-7 in patients aged less than 55 years, with a median of 9 months for 7-3 as compared with 17 months for 7-3-7 (P = .03). In older patients (aged <sup>3</sup> 55 years), 7-3-7 was more toxic, with significantly more severe (World Health Organisation (WHO) grade 3 or 4) stomatitis (P = .02) and no additional clinical benefit. Haematologic toxicity for induction courses was similar, with granulocytopenia < 0.5 x 10<sup>9</sup>/L for a median of 16 days per course for 7-3 and 15 days for 7-3-7. Haematologic toxicity was more severe for 5-2-5 consolidation courses (P = .003). Thus, induction therapy intensified with etoposide significantly prolonged remission.

To further assess the factors in induction that influenced outcomes like remission duration, the ALSG analysed the influence of dose and dose intensity (DI) of induction and consolidation chemotherapy in relapse rates in the above 264 de novo patients with AML.<sup>(11)</sup> Cox proportional hazards regression models were used throughout to identify prognostic factors, including dose delivery parameters, influencing the rate of relapse. Of 152 patients who achieved CR, 104 have relapsed with a median duration of CR of 15.8 months. Actual dose delivered was prospectively documented. Cox regression analysis identified the most significant prognostic factors jointly influencing duration of CR as performance status groups (p < 0.0001), percentage peripheral blasts (p = 0.0015), 7-3-7 arm (p = 0.0075), age < 40 years (p = 0.022) and induction dose cytarabine plus DNR (p

= 0.029). In this analysis patients randomised to the 7-3-7 arm had an estimated 43% reduction in the relapse rate, and each 10% reduction of doses cytarabine and DNR was associated with an estimated 45% increase in the relapse rate. The number of induction courses, delays in treatment and induction dose intensity did not significantly influence the duration of CR nor did any of the consolidation treatment parameters. These data suggest that the addition of etoposide and delivery of full induction doses of cytarabine and DNR were the most important treatment parameters influencing the duration of complete remission. A number of risk factors for induction outcome were examined.

Cytarabine (ara-C) has been an essential component of combination chemotherapy for induction of AML since Ellison et al first produced long-term survivors in AML.<sup>(12)</sup> The rationale for using a higher dose of cytarabine is that there appears to be a steep dose response curve for cytarabine in experimental tumour systems.<sup>(13,14)</sup> Patients whose myeloblasts formed and retained high levels of ara-C 5'-triphosphate had higher CR rates. Thus, high-dose cytarabine could overcome clinical drug resistance by this and other mechanisms.

Early clinical studies in AML suggested that high-dose cytarabine with amsacrine produced high response rates in refractory and heavily pretreated patients.<sup>(15)</sup> High-dose cytarabine has been successfully used in a number of combinations in relapsed patients and as post-induction therapy in phase I and II studies.<sup>(16-18)</sup> These studies provide a rationale for an intensified dose of cytarabine in induction chemotherapy for “*de novo*” patients.

The ALSG studied patients aged 15 to 60 years, presenting with newly diagnosed AML, who were randomised to receive either high-dose cytarabine, 3 g/m<sup>2</sup>/12 hourly on days 1, 3, 5 and 7 for 8 doses, DNR 50 mg/m<sup>2</sup>/days 1 to 3, etoposide 75 mg/m<sup>2</sup>/days 1 to 7 (HIDAC-3-7) or standard dose cytarabine 100 mg/m<sup>2</sup> continuous intravenous infusion for 7 days with daunorubicin and etoposide at the same dose and schedule as above (7-3-7).<sup>(19)</sup> Patients could receive a second or third induction course if CR was not achieved. All patients received the same post-induction consolidation therapy (5-2-5) for two courses. Eligible patients had no prior chemotherapy or myelodysplastic disease. Patients have been followed for a median of 4.5 years. Of 301 patients treated, CR was achieved in 71% with HIDAC-3-7 and 74% with 7-3-7. For patients in CR, the estimated median remission duration was > 45 months with HIDAC-3-7 and 12 months with 7-3-7 ( $p = 0.0005$  univariate analysis,  $p = 0.0004$  multivariate analysis). The estimated percentage of patients relapse free five years after achieving a CR was 49% on HIDAC-3-7, and 24% on 7-3-7. Patients in CR tended to survive longer with HIDAC-3-7 but there were no overall survival differences between the two arms. HIDAC-3-7 was associated with significantly more toxicity in induction with more leukopenia, thrombocytopenia, nausea and vomiting and eye toxicity (all  $p < 0.001$ ) but a similar incidence of severe CNS and cerebellar toxicity compared to 7-3-7. The consolidation treatment was the same in both arms but caused significantly more leukopenia and thrombocytopenia in patients previously treated with HIDAC-3-7 induction ( $p < 0.0001$ ). These data suggested that a dose-effect relation exists for cytarabine in AML and that HIDAC-3-7 prolongs remission duration and disease-free survival and is tolerable when used as initial induction therapy in patients with *de novo* AML.

The results of the ALSG trial are remarkably similar to those recently reported by Mayer et al using high-dose cytarabine as post-induction therapy.<sup>(20)</sup> In that study, patients in remission received 6 doses per course of high dose cytarabine, 3 g/m<sup>2</sup>, compared with an intermediate dose of 400 mg/m<sup>2</sup> and standard dose cytarabine of 100 mg/m<sup>2</sup>. Patients on high-dose cytarabine received 4 courses of 24 treatments. While only 56% of patients were able to complete the 4 courses of high-dose cytarabine, more cytarabine was given in Mayer's study than in the ALSG study. In Mayer's study, high-dose cytarabine significantly improved disease-free survival and overall survival when compared to conventional dose cytarabine. The disease-free survival of patients on high-dose cytarabine was 44% at 4 years for patients aged <sup>2</sup> 60 years, censoring patients who received bone marrow transplant. In the ALSG study, the disease-free survival at 4 years was 41% overall for patients on HIDAC-3-7. Censoring for marrow transplant patients, the disease-free survival was 39% at 4 years. Comparing HIDAC-3-7 and 7-3-7, the hazard ratio for disease-free survival was 0.64. In the study by Mayer et al, high-dose cytarabine post-induction resulted in similar hazard ratio for disease-free survival of 0.67.<sup>(20)</sup>

The results of these two studies compare favourably with those of autologous bone marrow transplantation with relapse-free survival rates of 25-50% at 3 years.<sup>(21)</sup> They may compare favourably with 50% relapse-free survival seen with allogeneic transplantation if selection factors such as age, performance status, length of time after complete remission and tolerance to previous therapy are taken in account.<sup>(22)</sup> Mayer et al reported few relapses after 20 months, but only further follow-up will determine if the remissions noted are as durable as seen with transplantation.

A three-arm post-induction trial by the Eastern Cooperative Oncology Group (ECOG) compared a single course of high-dose cytarabine, 3 g/m<sup>2</sup> for 12 doses plus amsacrine, weekly standard-dose cytarabine plus 6-thioguanine and allogeneic bone marrow transplantation.<sup>(23)</sup> The event-free survival at 4 years for patients aged less than 60 years in CR who received high-dose cytarabine and amsacrine was 28% (s.e. 11%). There was no difference in outcome in the ECOG subset of patients aged less than 41 years treated with either high-dose cytarabine, amsacrine or allogeneic bone marrow transplantation, although only 83 patients were compared. The results with a single course of high-dose cytarabine appear inferior to our results and to those reported by Mayer and colleagues.<sup>(20)</sup>

It is clear from a number of studies that the benefits of intensified therapy in AML are confined to younger patients.<sup>(10,16,20)</sup> In patients on the ALSG study receiving the three-drug combination with etoposide (7-3-7), the prolongation of relapse-free survival and survival advantage seen over a standard two-drug therapy was confined to patients aged less than 55 years.<sup>(10)</sup> Mayer et al stratified their patients according to age, reported no benefit in patients over 60 years of age and could not deliver high-dose cytarabine in that older age group.<sup>(20)</sup> The ALSG study was age limited, but younger patients fared better with higher response rates and lower toxicity. Thus, intensive therapy cannot be generally recommended for older patients.

A more fundamental question raised by the high-dose cytarabine studies is, when in the chemotherapy cascade should therapy in AML be intensified?<sup>(20,23,24)</sup> Treatment could theoretically be intensified during the induction phase, immediately after remission,

or after two to three months of preparative regimens, as in some transplantation programs. The advantages of giving intensive therapy to a patient in remission are that the marrow contains a normal proportion of haematopoietic cell progenitors and the patient's general condition is better. Thus, intensive treatment is better tolerated and less dangerous during remission than during induction. However, 30 to 40% of patients on standard regimens never have a remission and will never have the chance to benefit from improved intensified therapies that may develop in the future. Other curable tumours, such as testicular cancer and some lymphomas, appear to benefit from optimal initial treatment. Doses of cytarabine that are less high may be required when used in 8 doses in induction, as in the ALSG study, compared to the planned 24 doses used in the study by Mayer et al. The disadvantage remains the initial toxicity of intensified induction.

Regardless of its optimal position in the chemotherapy program, it is now clear that a dose-response relationship exists for cytarabine in AML. This has important implications for designing new optimal induction and post-induction therapies and for preparative regimens for transplantation.

It is clear that using a morphology of bone marrow with < 5% blasts to define CR is inadequate. Classification of CR should include cytogenetic CR or molecular CR. Further, a model of cell kill can be developed where remission duration is a useful clinical endpoint to study the effect of new induction treatment on resistant leukemia.

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