

# **Role of maintenance therapy in Acute Myeloid Leukaemia**

## **Study 1**

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Impact of Addition of Maintenance Therapy to Intensive Induction and Consolidation Chemotherapy for Childhood Acute Myeloblastic Leukemia: Results of a Prospective Randomized Trial, LAME 89/91

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### **Study design**

This was a prospective randomised multi-centre study that extended from December 1988 to June 1996

Randomisation methodology was not specified. Written informed consent was obtained for all patients.

Complete remission [CR] was defined as < than 5% blasts in a normocellular bone marrow with no evidence of extra-medullary leukaemia and normal blood counts.

### **Objectives**

The aim of this study was to assess the role of maintenance therapy in the treatment of childhood Acute Myeloid Leukaemia [AML]

### **Details of the study**

Previously untreated children and adolescents with AML of French-American-British [FAB] subtype M1 – M6 were included in the study. Patients with Down's syndrome, secondary AML, FAB subtype M0 or M7 AML or bi-phenotypic leukaemia were excluded from trial.

Induction therapy consisted of 7 days of continuous intravenous [IV] infusion of cytosine arabinoside [ARA-C] (200 mg/m<sup>2</sup>/day) and 5 days of IV mitoxantrone (12 mg/m<sup>2</sup>/day). Children less than 1 year received two thirds of these doses. Patients, who had more than 20% blasts in the bone marrow on day 20, received a second course of continuous IV infusion of ARA-C (200 mg/m<sup>2</sup>/day x 3 days) and IV mitoxantrone (12 mg/m<sup>2</sup>/day x 2 days). All patients in CR with an HLA-identical family donor underwent allogeneic bone marrow transplantation. Patients with no matched family donor received 2 courses of consolidation chemotherapy.

The first consolidation course consisted of 4 days each of IV etoposide (100 mg/m<sup>2</sup>/day as 1 hour infusion), IV ARA-C (100 mg/m<sup>2</sup>/day as continuous infusion) and IV daunorubicin (40 mg/m<sup>2</sup>/day as a 1 hour infusion).

The second consolidation course [only after complete haematological recovery] comprised of 2 cycles of ARA-C infusions plus asparaginase administered 7 days apart (cycle 1 – ARA-C 1 gm/m<sup>2</sup> 1 hour IV infusion 12 hourly x 4 followed by 6000 U/m<sup>2</sup> of asparaginase). All children above the age of 1 also received a 1-hour IV infusion of amsacrine (150 mg/m<sup>2</sup>/day) on days 4, 5 and 6 between the 2 cycles of ARA-C.

Maintenance therapy [MT] commenced after the second consolidation course, and consisted of daily oral 6-mercaptopurine (50 mg/m<sup>2</sup>/day) and monthly pulses of subcutaneous ARA-C [25 mg/m<sup>2</sup>/dose 12 hourly x 4 days] for 18 months. In March 1991, children still in CR after the second consolidation course were randomised either to stop or continue MT for 18 months. Randomisation to stop or continue therapy was centrally performed only after haematological recovery.

Patients with FAB subtypes of AML M4 and M5 or patients with a presenting white blood count [WBC] > 50 x 10<sup>9</sup>/L also received pre-symptomatic central nervous system [CNS] intrathecal [IT] chemotherapy. This comprised of 2 doses of ARA-C, methotrexate and corticosteroid during induction [day 1 and at haematological recovery] and 3 doses during consolidation therapy [days 1, 5 and 20]. Additionally, all patients who had evidence of CNS disease at diagnosis also received 3 additional courses of IT chemotherapy [2 during induction and 1 in consolidation] plus 24Gy cranial irradiation after the second consolidation course.

The main outcome measures were disease free survival [DFS] and overall survival [OS].

### **Patient characteristics**

Of the 268 patients were enrolled in the trial, 33 [12%] were below the age of 1. 28 [10%] patients had CNS disease at diagnosis. The median presenting WBC count was  $25.6 \times 10^9/L$ . Distribution of FAB AML subtypes were as follows: M1 [n=34], M2 [n=77], M3 [n=17], M4 [n=40], M4<sub>EO</sub> [n=16], M5 [n=77] and M6 [n=7]. Patient numbers according to treatment arms are shown in Fig 1

Of 139 patients eligible to commence MT, only 70 were randomised to either stop [n=34] or continue MT [n=36] for 18 months. Patient characteristics in the 2 randomised arms are shown in Table 1. Of the remaining 69 patients, 34 were non-randomly allocated to stop therapy [parental or physician choice –19, poor haematological recovery – 8 & pilot phase of study – 7] and 35 non-randomly allocated to MT [parental or physician choice – 13 & pilot phase of study – 22].

### **Outcome**

225 [84%] patients achieved CR after the first course of induction and an additional 16 achieved CR after reinforcement at day 21. The 6 year DFS and OS for the entire cohort was  $53\% \pm 6\%$  and  $60\% \pm 6\%$  respectively.

Comparing the DFS and OS for the randomised patients, the 6 year DFS was  $50\% \pm 15\%$  for patients randomised to MT versus  $60\% \pm 19\%$  in the stop arm [ $p = 0.25$ ] while the 6-year OS was  $58\% \pm 15\%$  in the MT group versus  $81\% \pm 13\%$  in the stop arm [ $p=0.04$ ] [Fig 2]. Table 2 shows the patient characteristics of relapsed patients in the 2 randomised arms.

As shown in table 3, patients randomised to the stop arm had a higher probability of achieving a second CR compared to patients randomised to MT [ $p=0.03$ ].

When DFS and OS were compared for the whole group [randomised and non-randomised], once again patients who received MT had a poorer outcome [DFS in

the MT group – 50% ± 11% vs. 63% ± 12% in the stop arm; p= 0.48 and OS in the MT group – 59% ± 11% vs. 73% ± 11% in the stop arm; p=0.08]. The probability of achieving a second CR was lower in the group who received MT [14/34] compared to the stop arm [19/28] [p=0.04]

### **Toxicity**

One randomised patient in the MT group died of fulminant hepatitis during MT.

### **Conclusions**

1] Maintenance therapy had an adverse impact with regard to OS in children with AML due to inferior salvage rate after relapse.