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TREATMENT OF ACUTE MYELOID LEUKAEMIA WITH EARLY INTENSIVE INDUCTION THERAPY

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Abstract

Patients with primary acute myeloid leukaemia were treated with induction therapy consisting of daunorubicin 50 mg/m^2 (days 1 and 2) and continuous cytosine arabinoside 400 mg/m^2 (days 1–5) with a 7–10-day gap between courses. Consolidation therapy consisted of one further similar course and a final course of cytosine 1 g/m^2 infusion (days 1–5). Patients were randomised to receive no further treatment or monthly maintenance therapy consisting of thioguanine 100 mg/m^2 twice daily and etoposide 100 mg/m^2 twice daily (days 1–5) alternating with CCNU 50 mg/m^2 once to a total of 6 courses. 64 patients entered the study; median age was 54 years (range 18–74 years) and 51 patients entered complete remission (79.7%). Thirty-two patients completed consolidation and were randomised between maintenance therapy (n=16) and no treatment (n=16). 21 patients have relapsed with neither remission duration nor relapse rate being affected by maintenance therapy.

Key words: Acute myeloid leukaemia; induction therapy, maintenance therapy, daunorubicin, cytarabine, thioguanine, etoposide, CCNU, randomised trial.

Conventional treatment for acute myelogenous leukaemia (AML) is generally held to consist of cytosine arabinoside 200 mg/m^2/day for 7 days with daunorubicin 45–75 mg/m^2/day for 3 days (3). In 1983 a collaborative group of haematologists in the South West of England decided to initiate a study of shorter courses of treatment and to try to obtain more intensive treatment by both increasing the dose of cytosine and also shortening the intervals between the courses (5). It was further wished to test the effect on survival and remission duration of maintenance therapy. The results obtained in a multicentre study of 64 patients accrued over two and a half years are presented below.

Material and Methods

Study group. The haematologists who contributed patients to the study are Dr Phillip Kingston and Dr Janet Ropner (Gloucester), Dr Robert Slade (Southmead Hospital, Bristol), Dr Phillip Whitehead (Frenchay Hospital, Bristol), Dr Geoffrey Scott (Bristol Royal Infirmary), Dr Stephen Johnson and Dr Malcolm Phillips (Taunton and Yeovil), Dr Miles Joyner (Exeter), Dr Brian Attock (Barnstaple), Dr Archie Prentice (Plymouth) and Dr John Morrell (Truro).

Patients. Sixty-four patients with previously untreated primary acute myelogenous leukaemia entered the study; 31 were male and 33 female and the group had a median age of 54 years (range 18–74 years). Sub-types of AML were classified by the French–American–British (FAB) classification (2). Registration in the trial was to a central secretariat and all patients were randomised at presentation to either proceed to receive maintenance therapy after completing consolidation or to stop treatment. During the period of the study a concurrent, unrelated epidemiology survey was being undertaken within the region (4). This survey registered 147 patients aged 18–75 years with AML during the study period. Three centres within the region regularly treated their patients in alternative trials, we therefore estimate that approximately half the patients with AML were entered into our study. Although a detailed analysis of the causes for exclusion (e.g. prior preleukaemic phase, previous chemotherapy or coincident malignant disease) is not available, the proportion is very similar to that observed by the Toronto Leukaemia Study Group in their analysis of consecutive patients with AML (9).

Treatment. Induction therapy consisted of 2 courses of daunorubicin 50 mg/m^2 on days 1 and 2, and cytosine arabinoside 400 mg/m^2/day by continuous infusion for 5 days with a 7–10-day gap between the courses; both courses of induction therapy were given without waiting

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to evaluate the effect of the first course. Complete remission was defined by standard criteria requiring recovery of adequate peripheral blood values (Hb >100 g/l, neutrophils $>1.0\times10^9$/l, platelets $>100\times10^9$/l, all unsupported by blood product transfusions) together with a normocellular bone marrow in which all cell lines were represented in normal numbers and with <5% blasts. Consolidation therapy after complete remission had been achieved consisted of a further course identical to the induction treatment followed after 3 weeks by a course consisting of cytosine arabinoside 1 g/m^2/day by continuous infusion for 5 days. Patients were then randomised to receive either no further treatment or maintenance therapy with monthly courses of thioguanine 100 mg/m^2 twice daily and etoposide 100 mg/m^2 twice daily for 5 days alternating with CCNU 50 mg/m^2 once to a total of 6 courses.

Supportive care. There was some variation in detail from centre to centre, but most patients were treated through tunnelled central venous lines in single rooms. Empirical intravenous antibiotics were given for febrile episodes and blood product support was given as required. The guidelines of the British Society of Haematology were taken as a minimum requirement by participating centres (1).

Results

Response and duration of response. Complete remission (CR) was achieved by 51 of 64 (79.7%) patients overall and unlike other multicentre studies (8) was not significantly less for patients over the age of 60 years (18 of 23, 78.2%). Three patients who had HLA matched siblings were referred for allogeneic marrow transplantation and are excluded from further analysis. The median duration of remission for the 48 evaluable patients who entered remission was 7.7 months with 18.75% continuing in CR. The median survival for 61 evaluable patients was 6.0 months with 14.75% alive at the analysis point 4 years from the start of the study.

Survival was not adversely affected by increasing age (Fig. 1). Curves for survival of patients aged 60 years or less and those for patients over 60 years are essentially identical. A survival advantage was demonstrated by FAB classification with acute myelomonocytic leukaemias (FAB-M4) showing a significantly better survival than acute myeloid leukaemia with differentiation (FAB-M2) at the $p<0.001$ level; this advantage was independent of remission rate. Other FAB groups contained too few patients to demonstrate variation in survival.

Maintenance therapy was given entirely on an outpatient basis and was not associated with any significant toxicity. No advantage to remission duration (Fig. 2) or survival was produced by maintenance therapy.

Reasons for failure. Complete remission was not achieved by 13 patients. One patient died within 7 days of starting treatment and so received an inadequate trial of therapy. Eight patients died of infectious complications

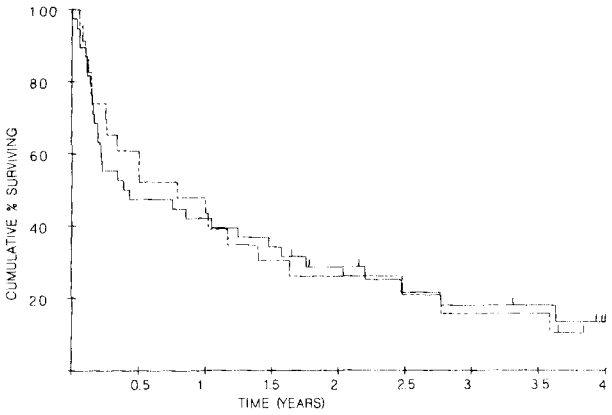

Fig. 1. Trial I. Survival by age. —— <60 years (n=38), - - - - - - >60 years (n=23). Difference not significant ($\chi^2=0.00$, p-value=0.99).

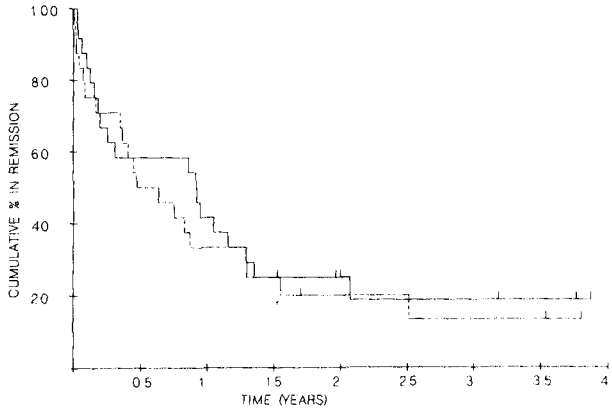

Fig. 2. Trial I. Survival with remission (uncensored). Maintenance therapy (——, n=24) versus no maintenance therapy (— - — - —, n=24). Difference not significant ($\chi^2=0.26$, p-value=0.61).

during the period of hypoplasia after initial therapy. Resistant disease, defined as significant residual leukaemia after 2 courses of treatment was seen for 4 patients.

A further 17 patients died while in complete remission. One patient died of drug toxicity (hepatotoxicity secondary to ketaconazole) and a further 3 patients died of causes unrelated to their disease or treatment (one myocardial infarction, one gastrointestinal haemorrhage in the presence of a normal platelet count and coagulation studies and one of carcinoma of the bronchus diagnosed over a year after complete remission). Thirteen patients died of infectious complications during periods of hypoplasia after consolidation therapy; both consolidation courses produced periods of pancytopenia for more than 21 days and in addition the final consolidation course of intermediate dose cytosine was consistently associated with moderate gastrointestinal toxicity.

Relapse of leukaemia has occurred in 22 patients and all have since died except one who received an allogeneic

marrow transplant in second complete remission. Eleven patients died without achieving a second complete remission and this group includes 2 patients with concurrent marrow and central nervous system (CNS) relapse. Unlike other studies (10) monocytic leukaemia was not a risk factor in developing CNS disease; the 3 affected patients in our study had FAB-M1 (n=1) or M2 (n=2) diseases. It was possible to obtain a second complete remission with chemotherapy for 11 patients; 7 patients were treated with combinations containing mitozantrone (7) and one with bisantrene (6); this group also includes one patient with marrow and CNS relapse.

Discussion

These results indicate that moderate increases above conventional dose rates combined with shortened intervals between induction courses of chemotherapy can produce high remission rates in a multicentre study of acute myeloid leukaemia which includes an appreciable population of older patients. Further comparable consolidation therapy was associated with a high incidence of deaths related to the long periods of treatment induced hypoplasia. Maintenance therapy as described was ineffective in preventing relapse or prolonging remission.

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