Multi Centre Study of a Combination of Fludarabine Phosphate, Cytosine Arabinoside and Granulocyte Colony Stimulating Factor (FLAG) in Relapsed and Refractory Acute Myeloid Leukaemia and in De Novo RAEB-t

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Introduction

The purpose of the present study was to evaluate the use of the FLAG regimen (fludarabine phosphate in combination with cytosine arabinoside and granulocyte colony stimulating factor (GCSF) in patients with poor risk myeloid malignancy. The rationale for this combination is based on the synergy between fludarabine phosphate and cytosine arabinoside; the cytotoxic activity of cytosine arabinoside is dependent on its intracellular conversion to its active metabolite the 5'-triphosphate (ara-CTP). The intracellular accumulation of ara-CTP is a multistep process, of which phosphorylation of ara-C to its monophosphate by deoxycytidine kinase (Cyd kinase) is the rate-limiting event. Fludarabine phosphate increases the activity of this critical enzyme leading to a higher rate of ara-CTP accumulation intracellularly (Gandhi [1]).

The rationale behind the addition of GCSF prior to administration of fludarabine phosphate and cytosine arabinoside is to increase the number of cells in the cell cycle which are vulnerable to cytosine arabinoside (Tafuri [2] and Gandhi [3]). Following the initial reports in 1994 by Estey [4] and Visan [5], the present multicentre study began to evaluate prospectively the response to FLAG in patients with RAEB-t and refractory and relapsed acute myeloid leukaemia (AML).

Patients and Methods

Patients

There were 19 U.K. centres involved in this study. At the inception of the study, it was decided that patients were to be divided into three groups for analysis of treatment results.

Group A. Patients with AML who had responded to first line chemotherapy and relapsed more than 6 months from the end of treatment.

Group B. Patients with AML who had responded to first line chemotherapy and relapsed within 6 months of stopping treatment or were resistant to first line chemotherapy.

Group C. Patients with de novo advanced myelodysplastic syndrome sub-type RAEB-t (refractory anaemia with excess blasts in transformation).
Objectives

The primary objective of the study was to evaluate the complete response rate to the FLAG regimen as remission induction treatment. Secondary objectives were to assess the survival time and to investigate the safety and tolerability of the FLAG regimen.

Eligibility

Patients had to be aged 18–75 years with a WHO performance status of 0–2. Specific exclusion criteria included de novo AML, previous chemotherapy for RAEB-t, chronic myeloid leukaemia in blast transformation, clinically significant impairment of renal or liver function and a prior bone marrow or peripheral blood stem cell (PBSC) transplant.

Treatment

Patients received induction therapy consisting of intravenous infusions of fludarabine phosphate given daily for five days (days 1–5) as a 30 minute intravenous infusion of 30 mg/m² 4 hours prior to each daily infusion of cytosine arabinoside. Cytosine arabinoside, at a dose of 2 g/m², was given daily for five days (days 1–5) as a 4 hour intravenous infusion. GCSF, at a dose of 30 million units, was given daily for seven days (day 1 through to day 6) by subcutaneous injection beginning 24 hours prior to the first administration of fludarabine phosphate.

Patients were assessed by bone marrow aspirate for remission status once neutrophil recovery was achieved, this being defined as an absolute neutrophil count of greater than or equal to 1 x 10⁹/l for three days. The use of GCSF as a supportive agent in the event of unsatisfactory neutrophil recovery post chemotherapy was allowed. After complete remission was achieved with patients having received one or two courses, up to two cycles of consolidation chemotherapy consisting of a four day course of FLAG (fludarabine and ara-C given for 4 days instead of 5) were recommended.

If complete remission was not achieved patients received a second cycle of induction chemotherapy at the clinician’s discretion. Patients who did not achieve a complete remission after two cycles of induction chemotherapy were withdrawn. Cytogenetic assessment was recommended in all patients. This was to be performed locally on a bone marrow aspirate, if possible, and the presence of a normal karyotype or any abnormal clone recorded.

Response to Treatment

A response to treatment was classified as complete remission if there were less than 5% myeloblasts in the bone marrow associated with evidence of trilineage regeneration and an absence of unequivocal leukaemic features. Survival data were analysed by the Kaplan-Meier method.

Results

89 patients were entered from the 19 centres (range 1–11), of whom 83 were eligible for the trial (21 – Group A, 44 – Group B and 18 – Group C). Reasons for exclusion were: untreated de-novo AML (3), non Hodgkin’s lymphoma (1), RAEB (1) and failed second line chemotherapy (1).

Patient Details and Response to Treatment

The median age of the eligible patients was 49 years (range 18–75); 25 patients were aged > 60 years. There were 42 male patients, 41 females. One patient died before study treatment, having given consent. Further details of the patients and the response to therapy, by disease group, are shown in Table 1. CR rates were 81% in Group A patients, 30% in Group B and 56% in Group C.

Cytogenetic Analysis

The protocol specified that all patients should have cytogenetic analysis attempted at trial entry; in 20 patients this was not done. It is noteworthy that of those with a successful analysis, only 5 had »favourable« karyotypes: