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A phase II trial of fludarabine in patients with previously treated chronic lymphocytic leukaemia

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Objectives. To evaluate fludarabine in patients with chronic lymphocytic leukaemia (CLL) not responding to standard treatment.

Design setting. Fludarabine was administered for 5 consecutive days and repeated 4-weekly.

Subjects. Seventeen patients at a single institution were treated.

Outcome measures. Objective remission was seen in 11 patients. The median survival time was 356 days.

Results and conclusions. Fludarabine is an effective treatment for patients with advanced CLL.

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Chronic lymphocytic leukaemia (CLL) is not a rare disease, and although it is not curable, most patients can be treated successfully for many years. When the disease becomes resistant to standard treatment, the prognosis becomes very poor and morbidity becomes significant. Although almost all patients with CLL initially respond to standard treatment, none are cured. The availability of new drugs to treat patients with CLL resistant to standard treatment is important in South Africa.

Fludarabine, an analogue of ara-adenine, has been shown to have activity in patients with CLL, with a response rate of 55% reported in patients with previously treated CLL.[1] In previously untreated patients, a response rate of more than 70% has been reported.[1,2]

The present study was undertaken, at a single institution, to evaluate fludarabine in patients with CLL not responding to standard treatment.

Patients and methods

Seventeen patients with CLL were entered into the study. Eligibility criteria included failure of previous treatment, performance status of 0 - 2 (ECOG performance status was used*), serum bilirubin ≤ 30 µmol/l and serum creatinine ≤ 114 µmol/l. Patients had to be free of active infection and had to give written informed consent. The Rai classification was used.†

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All patients had received prior chemotherapy as part of the eligibility criteria for entry into the study, and had relapsed while receiving chemotherapy. Patients had to have been off chemotherapy for at least 6 weeks before entry into the study, and most patients entered it 6 weeks after stopping the chemotherapy to which they were not responding. No patient had been off chemotherapy for longer than 12 weeks before entry. The 6 patients with early-stage disease had received chemotherapy and had progression of disease (i.e. all 6 were refractory to standard treatment).

Fludarabine 25 mg/m^2 was administered in 100 ml in 0.9% sodium chloride or dextrose 5% over 30 minutes daily for 5 consecutive days and repeated at 28-day intervals. Adjustments in dosage were made for haematological toxicity and for lethargy and somnolence. ECOG toxicity was used.[3]

Complete remission was defined as peripheral blood lymphocytes < 40% with total leucocyte count < 10 x 10^9/l; marrow lymphocytosis < 30%; haemoglobin concentration > 12 g/dl; and platelets > 100 x 10^9/l. Any previously involved lymph nodes were now to measure less than 1 x 1 cm^2. If the liver and or spleen had been involved, they were to have returned to normal size.

Partial remission was defined as reduction of the absolute lymphocyte level to < 15 x 10^9/l and by at least 50% of pretreatment values; a regression of at least 50% in the sum of the products of perpendicular diameters of at least 2 enlarged lymph nodes; a regression of splenomegaly by at least 50% of its extent below the left costal border; a regression of hepatomegaly by at least 50% of its extent below the right costal border; marrow lymphocytosis of 30 - 50% or a decrease of 50% from the previous level, whichever was greater; a haemoglobin concentration greater than 12 g/dl and platelets greater than 100 x 10^9/l; and an increase in haemoglobin concentration, platelets or granulocyte count by at least 50% of the deviation from normal of pretreatment values.

Results

All patients were evaluable for toxicity and response. Patient characteristics are shown in Table I.

Seventeen patients were entered into the study. The median time from diagnosis to entry on study was 24 months (range 3 - 126 months). The median haemoglobin concentration at entry was 13.25 g/dl (range 5.7 - 15.5 g/dl)

* Grade 0 — fully active, able to carry out all pre-disease performance without restriction; grade 1 — restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature; grade 2 — ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.

† Stage 0 — lymphocytosis in blood with lymphocyte count > 15 x 10^9/l and bone marrow populated with mature lymphocytes comprising > 40% of nucleated cells; stage 1 — same as stage 0 with lymphadenopathy; stage 2 — includes same degree of lymphocytosis as stage 0, plus enlarged spleen and/or liver; stage 3 — includes lymphocytosis and anaemia, defined as haemoglobin < 11 g/dl and haematocrit < 33% (physical findings of lymphadenopathy, hepato- or splenomegaly are not required, and no distinction with regard to type of anaemia, i.e. haemolytic or otherwise, is made); stage 4 — includes the findings at diagnosis of lymphocytosis as defined in stage 0, with thrombocytopenia (< 100 x 10^9/l) (again, any previous physical signs may be absent).

Table I. Patient characteristics

Total No. of patients	17
Sex	
Male	9
Female	8
Median age	61 years (range 46 - 78 years)
Performance status	
0	3
1	9
2	4
3	1
CLL stage	
I	1*
II	5
IV	11
Previous treatment	
One cytostatic regimen	12
Two cytostatic regimens	4
Three cytostatic regimens	1
Complete response	4
Partial response	7
No change	1
Progression of disease	5

* Patient had massive progressive lymphadenopathy.

(normal values for males 13 - 18 g/dl and for females 12 - 16 g/dl). The median absolute lymphocyte count was 19.53 x 10^9/l (range 1.1 - 182.01 x 10^9/l) (normal value 0.7 - 4.8 x 10^9/l); and the median platelet count was 103.5 x 10^9/l (range 24 - 349 x 10^9/l) (normal value 140 - 450 x 10^9/l).

Toxicity

Five patients experienced somnolence and fatigue; 2 had mild somnolence (grade 1) and 3 moderate somnolence (grade 2). No patient had severe somnolence or agitation, confusion, disorientation or hallucinations (grade 3), or comas, seizures or toxic psychosis (grade 4). Two patients developed skin rashes. One patient had an asymptomatic scattered macular, papular eruption (grade 1), and 1 had a generalised symptomatic macular, papular skin eruption (grade 3).

Six patients developed thrombocytopenia ascribed to treatment; 5 had a platelet count of $\geq$ 75.0 x 10^9/l, and 1 a platelet count of 25.0 - 29.9 x 10^9/l. In 2 patients a fall in the haemoglobin concentration necessitated blood transfusion. Six patients developed leucopenia, including 3 with a white blood count between 1.0 and 1.9 x 10^9/l (normal value 4 - 11 x 10^9/l), a granulocyte count between 0.5 and 0.9 x 10^9/l (normal value 1.5 - 8.8 x 10^9/l) and a lymphocyte count between 0.5 and 0.9 x 10^9/l (normal value 0.7 - 4.8 x 10^9/l).

It is not possible to make a meaningful statement about side-effects as a marker of efficacy owing to the small number of patients entered into the study.

Response

Four patients had a complete response (2 with stage II and 2 with stage IV CLL). Partial remission was documented in 7 patients (3 with stage II and 4 with stage IV CLL). One patient showed no change and in 5 the disease progressed.

The median time to treatment failure of the 11 patients who responded to treatment (4 complete and 7 partial responders) was 148 days. The 4 complete remissions lasted from 408 to 796 days. The median survival time was 356 days.

Although no finite conclusions can be reached about the observed median time to treatment failure and survival in a phase II study, it is probable that this time was longer than would be expected for treatment-resistant patients. The numbers are too small to comment on gender specificity.

Discussion

The toxicity of fludarabine in this group of patients with refractory CLL was acceptable, with somnolence the most common side-effect, while myelosuppression was documented in 13 of the 17 patients. The toxicities documented are in keeping with those previously reported. Eleven of the 17 patients had an objective response to treatment (complete plus partial response), with 4 having a complete response. Our response rate of 65%, median time to treatment failure of 148 days, and median survival of 356 days in patients with CLL no longer responding to standard treatment, compares favourably with figures reported by Keating *et al.*[1] and Bergmann *et al.*[4] The median survival time of patients with treatment-resistant CLL treated with fludarabine of 1 year constitutes a significant advance in the management of these patients. A Cooperative Intergroup Study in the USA comparing chlorambucil, fludarabine and chlorambucil plus fludarabine as front-line treatment has recently been completed. The results of this study will establish the role of front-line fludarabine treatment.

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