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Rapid control of chronic granulocytic leukaemia

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Summary

Sixty patients with chronic granulocytic leukaemia (CGL), anaemia, hyperleucocytosis and hepatosplenomegaly were randomized into 3 treatment schedule consisting of:

(i) cyclophosphamide 600mg/m^2 intravenously (IV) on day 1.
(ii) cytosine arabinoside 100mg/m^2 subcutaneously (sc) 12 hourly for days 1-5.
(iii) combination of IV cyclophosphamide 600mg/m^2 one day 1 and cytosine arabinoside 100mg/m^2 12 hourly sc for days 1-5.

Each cycle of treatment lasted 7 days.

Patients on combined chemotheraphy achieved laboratory and clinical remission within 28 days of treatment, while patients on single agent chemotheraphy of cytosine arabinoside or cyclophosphamide still had hyperleucocytosis and hepatosplenomegaly after 28 days of treatment.

Six patients treated with cyclophosphamide only had thrombocytopenic bleeding, but no patient treated with either cytosine arabinoside only or a combination of cytosine arabinoside and cyclophosphamide bled.

It is suggested that patients with CGL, anaemia, hyperleucocytosis, and hepatosplenomegally can be rapidly controlled with a combination of cytosine arabinoside and cyclophosphamide.

Résumé

Soixante patients, victimes de la leucémie granulocytique chronique (LGC) ainisi que de l'anémie, l'hyperleucocytose et l'hépatosplénomégale, affectés au hasard à trois groupes différents, ont suivi des soins médicaux de la manière suivante:

Groupe 1: — cyclophosphamide 600 mg/m^2 intraveineux (IV) pour le premier jour.
Groupe 2: — cytosine arabinoside 100 mg/m^2 sous-cutané (sc) toutes les 12 heures pour les jours 1-5.
Groupe 3: — une combinaison de cyclophosphamide 600 mg/m^2 intraveineux (IV) pour le premier jour et la cytosine arabinoside 100 mg/m^2 toutes les 12 heures (sc) pour les jours 1-5.

Chaque cycle de soins a duré de 7 jours.

Les patients du troisième groupe qui ont suivi la combinaison chémothérapeutique ont réalisé une rémission de laboratoire ainsi qu'une rémission clinique en moins de 28 jours alors que ceux soumis au seul agent chémothérapeutic de cytosine arabinoside ou de cyclophosphamide retenaient toujours l'hyperleucocytose et l'hépatosplénomégale aprés 28 jours de soins.

Six patients qui ont été soigné avec le cyclophosphamide avaient seulement un saignement thrombocytopénic, mais aucun patient soigné avec seule la cytosine arabinoside ou une combinaison de celle-ci et la cyclophosphamide n'a saigné.

Il est suggéré que les victimes de LGC et de l'anémie, l'hyperleucocytose et l'hépatosplénomégale peuvent être rapidement controllés avec une combinaison de cytosine arabinoside et le cyclophosphamide.

Introduction

Chronic granulocytic leukaemia (CGL) is a myeloproliferative disorder in which there is unrestrained proliferation of myeloid cells in the reticuloendothelial system. The myeloid cells are

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Philadelphia chromosome positive in 90% of cases and white blood cell (Wbc) count ranges between 50 x 10^9/L - 1000 x 10^9/L[1], though some asymptomatic cases have been diagnosed at counts lower than 50 x 10^9/L[2,3]. The degree of leucocytosis mirrors the extent of the disease.

Spiers[1] described three phases of the disease. The chronic phase is when the bone marrow produces erythrocytes, granulocytes and platelets that are normal. The disease responds well to a variety of non-intensive drug treatment, and good health and activity are maintained. Accelerated phase is when there is gradual failure of response to treatment and there may be failure of production of platelets, and this stage may last for months or as long as 1 to 2 years. Acute transformation is when the disease is not responsive to treatment and peripheral film and bone marrow show increase in blasts and promyelocytes which may constitute over 20% of nucleated cells[3].

Drugs used in the treatment of CGL include alkylating agents like busulphan, cyclophosphamide, mustine hydrochloride and melphalan[2,4] but busulphan has been the most widely used because it is effective and convenient[5]. Cytosine arabinoside has been employed as a single agent in the treatment of CGL on blastic transformation[6,7]. A combination of cyclophosphamide, cytosine arabinoside and radiotherapy have been employed as preoperative treatment for CGL patients undergoing bone marrow transplantation[8]. Mercaptopurine or thioguanine plus busulphan have been combined in the treatment of CGL[9].

In Nigeria, most cases of CGL present late with hyperleucocytosis[10,11] which leads to thrombo-embolic phenomenon causing blindness, priapism and deafness. Few cytotoxic drugs are available in Nigeria due to import restrictions and busulphan has not been available in the past 4 years and we rely on cyclophosphamide in the treatment of CGL which is less effective.

This study compares the use of cyclophosphamide and cytosine arabinoside as single agent and the combination of both drugs in the treatment of CGL.

Materials and methods

Sixty patients with CGL seen in Jos University Teaching Hospital between October, 1984 and September, 1989, were randomized into treatment schedules consisting of:

(i) cyclophosphamide 600mg/m^2 intravenously (IV) once weekly.
(ii) cytosine arabinoside 100mg/m^2 subcutaneously (sc) 12 hourly for days 1-5 in a week.
(iii) combination of cyclophosphamide 600mg/m^2 IV once weekly and cytosine arabinoside 100mg/m^2 12 hourly for days 1-5.

Allopurinol 100mg, 3 times daily, was given to all patients throughout the 28 days of treatment.

Diagnosis of CGL was based on a Wbc count of over 50 x 10^9/L with a left shift consisting of myeloblasts, promyelocytes, metamyelocytes and mature forms. Bone marrow aspiration was carried out in all cases and myelogram performed. A diagnosis of CGL in chronic phase was made where a combination of myeloblasts and promyelocytes was less than 10% in the bone marrow and peripheral film[5]. Leucocyte alkaline phosphatase score was performed on the samples but chromosomal analysis was not performed due to lack of facilities.

The haematocrit (Hct), Wbc count and platelet count were determined prior to drug administration. Also the spleen and liver sizes were measured in cm along the mid-clavicular line from the coastal margin to the lowest edge of the organs. These haematological indices and organ measurements were determined at weekly intervals during the treatment period. Treatment was discountinued as soon as the Wbc count dropped to 15 x 10^9/L.

Measurements recorded for the treatment groups were compared by means of students' *'t'* test. Regression analysis was carried out for the main value of the parameters measured against time. This gave the line of best fit and the slope which represents the rate of such parameters per day.

Results

The patients were randomized into 3 treatment groups; cyclophosphamide only, cytosine arabinoside only and cyclophosphamide plus cytosine arabinoside. In each of the groups there were 13 males and 7 females. The mean age for the cyclophosphamide group was 39.5 years, the cytosine arabinoside group 38.4 years and the combination group 39.1 years. The range of leucocyte alkaline phosphate score in the subjects was 11 ± 7. The main clinical features were hepatosplenomegaly, bone pain and fever.

At the beginning of therapy, the mean Wbc count (Fig. 1), platelet count (Fig. 2) liver size (Fig. 3) and spleen size did not differ significantly from one another ($P > 0.5$).

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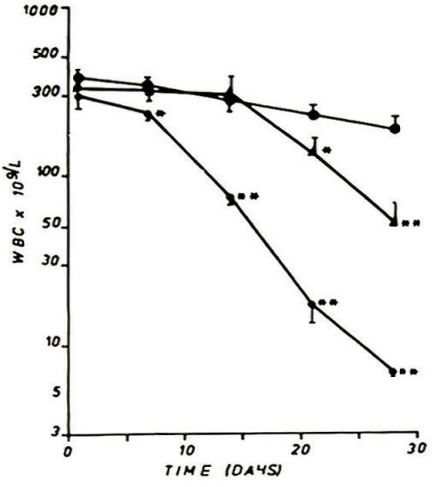

Fig. 1: Mean white blood cell count (WBC) of patients treated with cyclophosphamide (O, n = 20); cytosine arabinoside (Δ, n = 20) or cyclophosphamide plus cytosine arabinoside (⊖, n = 20). Vertical lines show s.e. mean.
Note that the ordinate is a log scale
* $0.05 > P > 0.01$
** $P < 0.01$ by students' unpaired t-test.

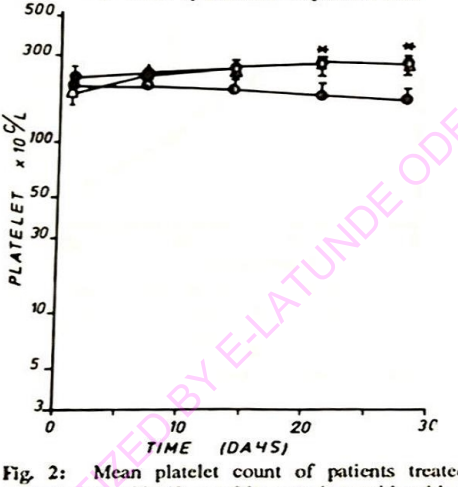

Fig. 2: Mean platelet count of patients treated with cyclophosphamide (O, n = 20); cytosine arabinoside (Δ, n = 20) or cyclophosphamide plus cytosine arabinoside (⊖, n = 20) determined every 7 days. Vertical lines show s.e. mean.
Note that the ordinate is a log scale
* $0.05 > P > 0.01$ by students' unpaired t-test.

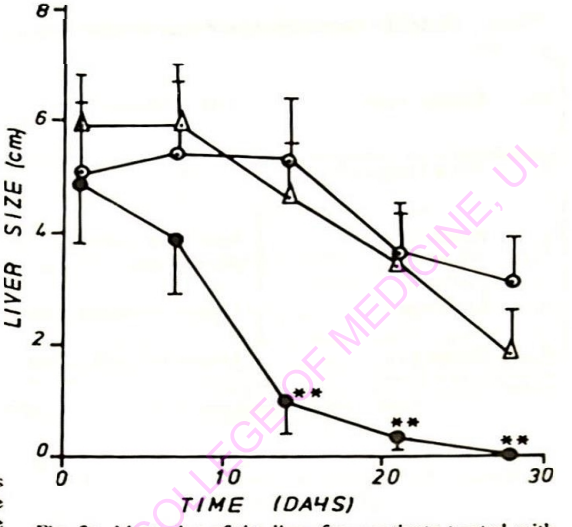

Fig. 3: Mean size of the liver from patients treated with cyclophosphamide (O, n = 20); cytosine arabinoside (Δ, n = 20) or cyclophosphamide plus cytosine arabinoside (⊖, n = 20) measured every 7 days. Vertical lines show s.e. mean.
** $P < 0.001$ by students' unpaired t-test.

On presentation, the Hct values for the patients in the 3 groups did not differ significantly ($P > 0.05$) from one another. The Hct value of 0.28 ± 0.02 L/L for each group did not change significantly ($P > 0.05$) following treatment for 28 days.

The Wbc count showed slight reduction in the 3 groups by day 7 but by day 14 the patients on cytosine arabinoside had significantly lower count than those on cyclophosphamide ($P < 0.05$) and this was maintained for the last 14 days of treatment. The group on combination chemotheraphy of cyclophosphamide and cytosine arabinoside achieved lower Wbc counts than the groups on either of the drugs alone ($0.05 > P > 0.01$) from day 7-28 of treatment. Regression analysis of the mean Wbc values for the 3 groups showed that they were falling at different rates per day (Table 1) (7337 cells/day for cyclophosphamide, 9,166 cells/day for cytosine arabinoside and 11,430 cells/day for cyclophosphamide plus cytosine arabinoside group).

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Table 1: Rates of change of some measured variables in patients on different cytotoxic chemotherapy

No.	Measurement	Type of Change	Rate of Change/Day		
			Cyclophosphamide	Cytosine Arabinoside	Cyclophosphamide with Cytosine Arabinoside
1.	White Blood cell count	Number of cells reduced/day	7,337	9,166	11,430
2.	Platelet count	Number of platelet reduced (↓) or increased (↑)/day	1,218 ↓	2,870 ↑	2,778 ↑
3.	Liver size	Length (cm) reduced/day	8.08	0.12	0.20
4.	Spleen size	Length (cm) reduced/day	0.19	0.21	0.51

Note Values indicate rate of change per day as determined from the linear regression analysis.

The administration of cyclophosphamide caused a progressive fall in platelet count while either cytosine arabinoside alone or in combination with cyclophosphamide increased the platelet count to a similar extent. The differences in platelet count were only significant ($0.05 > P > 0.01$) from day 14 to 28 (Fig. 2).

Regression analysis showed a fall in platelet count of 1,218 platelets per day for the cyclophosphamide group while it increased by 2,970 per day for cytosine arabinoside group and 2,778 for the group on cyclophosphamide plus cytosine arabinoside.

From day 1-7 of therapy, the size of the spleen in the three groups were similar but thereafter the size of the spleen for the cyclophosphamide group was larger than those on cytosine arabinoside only ($P < 0.05$) or combination chemotherapy group ($P < 0.05$; Fig. 4).

For each treatment group, 14 out of the 20 patients presented with hepatomegaly. The reduction in the size of the liver that occurred with each modality of treatment is shown in Fig. 3.

Six of the 20 patients treated with cyclophosphamide only had a platelet count of 185 ± 30 x 10^9/L on presentation. The count fell to 75 ± 15 x 10^9/L within the period of treatment. This thrombocytopenia resulted in bleeding in this group of patients. Thrombocytopenic bleeding resulting from treatment did not occur in the other groups. thrombocytopenia resulted in bleeding in this group of patients. Thrombocytopenic bleeding resulting from treatment did not occur in the other groups.

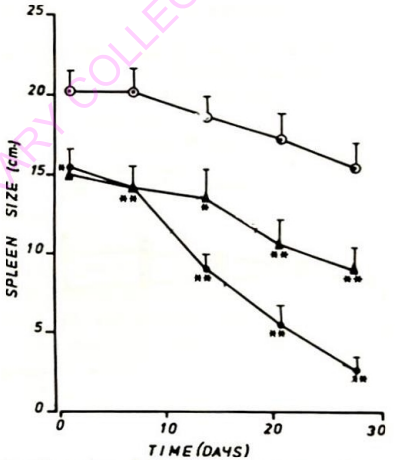

Fig. 4: Mean size of the spleen (cm) from patients treated with cyclophosphamide (O, $n = 20$); cytosine arabinoside (Δ, $n = 20$) or cyclophosphamide plus cytosine arabinoside (O, $n = 20$) measured every 7 days.
Vertical lines show s.e. mean.
* $0.05 > P > 0.01$
** $P < 0.01$ by students' unpaired t-test.

Discussion

Chronic granulocytic leukaemia (CGL) in Nigeria presents with anaemia, hyperleucocytosis and hepatosplenomegaly because cases present late to the clinician[10,11]. Results from patients on their first presentation during the present study are consistent with such trends in Nigeria. Such late presentations with marked hyperleucocytosis may lead to sensorineural hearing impairment, loss of vision and priapism, such that its rapid control becomes imperative.

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Busulphan, an alkylating agent, is the most widely used drug in the treatment of CGL[5] although it requires 3 months of treatment to control the disease[2]. This drug is hardly available in Nigeria, and cyclophosphamide, an alternative agent, may take 12 weeks to control CGL in patients with mean leucocyte count of 100 x 10^9/L[4]. Cytosine arabinoside, a synthetic pyrimidine antimetabolite that inhibits DNA synthesis, has been employed in the treatment of CGL on blastic transformation[6,7] and has also been combined with cyclophosphamide and radiotherapy for preoperative treatment of CGL patients undergoing bone marrow transplantation[8].

Various techniques have been investigated for the rapid control of CGL. Leucapheresis may reduce the Wbc count and organomegaly rapidly[12] but the equipment is not available in our centre. Mercaptopurine or thioguanine plus busulphan have been combined in the treatment of CGL[9]. The principle of combination chemotherapy has been employed in the present study with the objective of achieving rapid control of CGL. Where a single agent like busulphan, cytosine arabinoside or cyclophosphamide is used in treating the advanced cases of CGL seen in Nigeria, there may be no visible alteration in the haematocrit (Hct), Wbc count, platelet count and organomegaly in the first 14 days of treatment. Sensorineural hearing impairment and loss of vision may occur while the patient is undergoing treatment with these agents[11]. Results from the present study show that the disease was still prominent in patients on either cyclophosphamide or cytosine arabinoside only, after 28 days of treatment. The control of the features was not appreciable during the first week of treatment but became pronounced thereafter. Haematocrit improved but did not get to the normal value in the Nigerian community[13]. From the result of this study, we suggest that cytosine arabinoside and cyclophosphamide act synergistically in the rapid control of CGL. The 3 groups of patients were treated with allopurinol which has been reported to potentiate the effect of cyclophosphamide[14].

The advantage of the introduction of cytosine arabinoside in the management of CGL in this study is its effect on platelet count. It was reported that cyclophosphamide is preferred in CGL cases where thrombocytopenia is a presenting feature[2]. In this study 6 of the 20 patients treated with cyclophosphamide only developed thrombocytopenic bleeding. Indeed, the platelet count of this group of patients, progressively declined while the platelet count of patients on cytosine arabinoside only and combination of cytosine arabinoside and cyclophosphamide continued to increase with time such that none of the patients in the two regimens manifested haemorrhagic symptom. It is suprising that the combination increased platelet count while patients on cyclophosphamide only developed thrombocytopenia.

The findings of this study suggest that CGL patients with anaemia, hyperleucocytosis, and massive hepatosplenomegaly should be treated with a combination of cytosine arabinoside and cyclophosphamide. This mode of therapy rapidly controls the clinical and laboratory features of CGL better than single agent chemotherapy.

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