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ORAL IDARUBICIN IN THE TREATMENT OF ACUTE MYELOGENOUS LEUKAEMIA AND THE BLAST PHASE OF CHRONIC MYELOID LEUKAEMIA

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SUMMARY

Fourteen patients with poor-risk acute myelogenous leukaemia (AML) and five patients with accelerated phase/blast crisis chronic myeloid leukaemia (CML) were treated with 3 days of oral idarubicin (25 mg/m^2/day). No complete remissions or return to chronic phase CML were observed. A fall in the peripheral blast count was seen in all patients with the first cycle of treatment, and with subsequent cycles in CML patients, but all responses were transient, with eventual reemergence of peripheral blasts. In some patients, there was a clear cut improvement in symptoms such as bone and splenic pain. Five of the AML patients and all of the CML patients were treated as out-patients. In this group of patients oral idarubicin was found to be a useful drug for palliative treatment.

KEY WORDS Idarubicin Acute myelogenous leukaemia Chronic myeloid leukaemia

INTRODUCTION

The anthracycline antibiotics are a major component of combination chemotherapy regimes in the treatment of acute leukaemia (Schwartzenberg, 1975). The standard anthracyclines adriamycin and daunorubicin can however only be given intravenously. An analogue of daunorubicin, 4-demethoxydaunorubicin (IDARUBICIN), has been shown to have antitumour activity after oral and intravenous administration (DiMarco *et al.*, 1977). Subsequently it has been shown that intravenous idarubicin has significant activity as first line treatment in acute leukaemia (Berman *et al.*, 1987), and in patients for whom standard combination chemotherapy regimes have failed (Daghestani *et al.*,1985; Harousseau *et al.*, 1987). The latter observation is in keeping with experimental data suggesting that idarubicin is active against relatively anthracycline-resistant tumours (Casazza *et al.*, 1980a). Furthermore, idarubicin has been shown to be less cardiotoxic than other anthracyclines (Casazza *et al.*, 1979, 1980b).

These properties of idarubicin suggested that it would be a useful drug for the treatment of leukaemia in poor risk patients with acute leukaemia. A phase II trial of oral idarubicin was therefore conducted. The results are presented below.

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MATERIALS AND METHODS

Treatment

A treatment course of idarubicin, (total dose 75 mg/m^2), was given orally at a dose of 25 mg/m^2 daily for three days. The interval between courses was determined by the clinical status of the patients and the peripheral white cell count.

Patients

Acute myelogenous leukaemia (AML)

There were 14 patients (nine male: five female) with AML. The mean age of the group was 57 years (range = 18–81 years). Seven patients had primary AML, and had originally received standard adriamycin based combination chemotherapy. Five of these had relapsed after being in complete remission and two had resistant leukaemia. The remaining seven patients developed AML on a background of myelodysplasia. Five patients in this group had received combination chemotherapy (with no complete remissions), and two were previously untreated. Leukaemic blasts were present in the peripheral blood of all patients prior to treatment and ranged from $0{\cdot}23 \times 10^9$/l to 132×10^9/l (mean = 48×10^9/l). The total peripheral white cell count ranged from $7{\cdot}7 \times 10^9$/l to 150×10^9/l (mean 77×10^9/l).

Chronic myeloid leukaemia (CML)

Five patients (three male: two female) with CML in accelerated phase or blast crisis were treated. The mean age of the group was 47 years (range 32–57 years). All but one patient had been previously treated with one or more drugs, e.g. busulphan, hydroxyurea, mitobromitol, and had become refractory to treatment. Prior to the first course of idarubicin, the mean total white cell count in this group was 108×10^9/l (range 28–309×10^9/l). Two patients had overt blast crisis, one with mixed megakaryoblastic/erythroid blasts and the other myeloid blast crisis. The other three patients had CML in accelerated phase at the time of commencing treatment with idarubicin.

Baseline investigations

All patients had a full blood count, bone marrow examination, urea and electrolytes, serum uric acid and liver function tests and electrocardiographs prior to starting treatment.

RESULTS

AML

No complete remissions were achieved. A fall in total white count starting as early as day 3 of treatment was seen in all patients. The lowest white cell count reached ranged from $0{\cdot}2$–$3{\cdot}9 \times 10^9$/l (median $1{\cdot}32 \times 10^9$/l). Circulating blasts were absent in all but two patients during the period of cytopenia. However, responses were transient, with eventual reappearance of circulating blasts. All patients required blood transfusions (2–4 units/cycle) after idarubicin treatment. The platelet count fell in all patients and platelet transfusions were required in nine patients. Two patients were retreated with idarubicin. One died during the second course with septicemia. The other patient received three courses of idarubicin before eventually becoming resistant (Figure 1). Survival ranged from 11 days to 150 days, with a median of three weeks.

There were three deaths during the period of cytopenia, two due to septicemia and one due to intracranial hemorrhage, despite a platelet count of $> 30 \times 10^9$/l in this patient. Eight patients survived for 3 weeks or more after starting treatment. Two of these received further chemotherapy

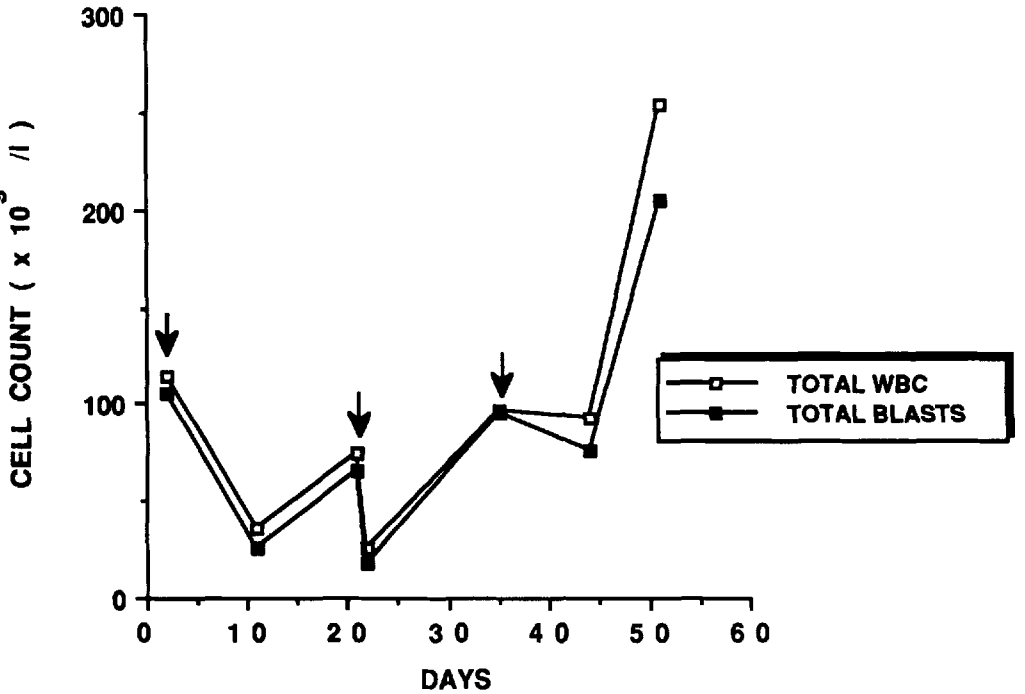

Figure 1. Peripheral WBC in AML patient given 3 courses idarubicin (arrows)

(one with adriamycin 25 mg/^{2}m d 1–3 and cytosine arabinoside 100 mg/^{2}m d 1–7, and the other with high dose cytosine arabinoside 1 gm^2/m d 1–6), but both died with resistant leukaemia.

No abnormalities in liver function tests or clinically overt cardiotoxicity were noted in any patient. Four patients experienced moderate nausea and vomiting which responded to prochlorperazine. Nine of the 14 AML patients were able to start treatment at home. Five were able to remain out of hospital even during the period of maximum myelosuppression. The rest required hospital admission for management of myelosuppression related complications.

CML

Complete remission or return to chronic phase CML was not achieved. A fall in total white cell count, and blast count was seen initially in all patients. The nadir white cell count ranged from 0·1–3·7 $\times$ 10^9/l and the nadir platelet count from 7–726 $\times$ 10^9/l. The time taken to reach the lowest white count ranged from 14–33 days (mean 21 days). All patients required blood transfusions (2–4 units/cycle) during each cycle of treatment. Platelet support was required in only two of the patients (five cycles) with low pretreatment platelet counts ($>40 \times 10^9$/l), prior to idarubicin therapy. The five patients received 2, 2, 4, 5 and 6 cycles respectively.

The changes seen in total white cell count and blast count in one of the patients are shown in Figure 2. This patient had Philadephia positive (Ph+ve) CML with a megakaryocyte/erythroid blast crisis. Prior to treatment she was anemic and jaundiced, with gross splenomegaly (20 cm) and splenic and diffuse bone pain. Within 4 days of starting idarubicin the pain receded dramatically and the spleen size decreased to 15 cm below the left costal margin. On day 30 of the first treatment cycle, she underwent a splenectomy. She received six courses of idarubicin, at intervals ranging from 14–27 days.

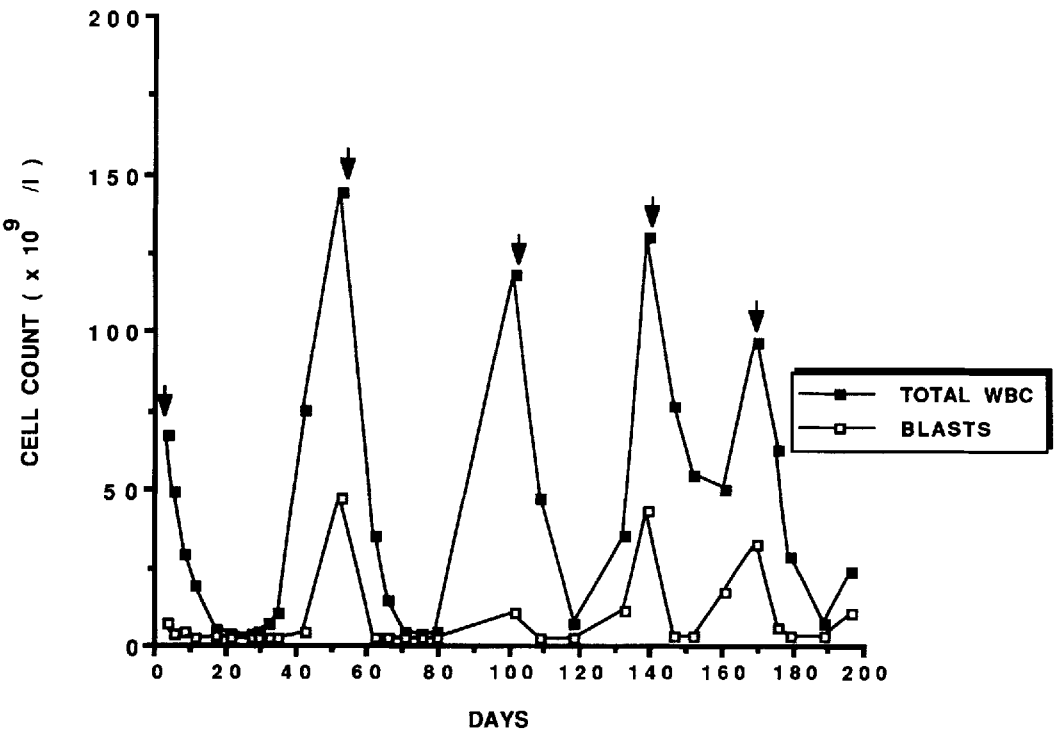

Figure 2. Peripheral white cell count and blast count in patient with megakaryocytic/erythroid blast crisis treated with idarubicin (arrows)

After the sixth course of treatment she became septicemic and thrombocytopenic. She recovered and was subsequently managed with five single oral doses of idarubicin (25 mg/m^2) given approximately every four weeks. This led to stabilization of the peripheral white cell count in the range of 50–60 × 10^9/l. She died 15 months after starting idarubicin with bronchopneumonia.

Five patients survived 11, 12, 20, 23 and 60 weeks after starting treatment.

No abnormalities in liver function tests or overt cardiotoxicity were seen with repeated courses of treatment in these patients. Alopecia did not occur in any patient. Mild to moderate nausea and vomiting was noted in nine out of 19 treatment courses and was controlled by standard doses of prochlorperazine. Fatigue was noted by all patients during the first week of treatment. One patient consistently noted 'flu-like' symptoms (myalgia, joint pain) after idarubicin and received prophylactic paracetamol with subsequent courses. All the patients were treated from home, and two patients were able to return to work for a period of time.

DISCUSSION

Oral idarubicin has been reported to lead to complete remission in a proportion of patients with resistant or relapsed AML (Parapia *et al.*, 1987; Lowenthal *et al.*, 1988). This study was designed to investigate the use of oral idarubicin in a group of poor-risk patients with AML and CML accelerated phase or blast crisis for whom cure was not a realistic objective. None of the patients in the study went into complete remission (or returned to chronic phase CML). However, a decrease in the peripheral white cell and blast count was seen with the first course of idarubicin in AML

patients and with subsequent courses in CML patients. Although subjective improvement in symptoms is notoriously difficult to assess, there was no doubt that in at least two patients, the symptoms associated with a high peripheral leukaemic blast count, (e.g. bone pain) were markedly improved with idarubicin. Overall, the toxicity of the drug was low, and treatment could be administered on an out-patient basis. This was particularly useful in the patients with CML, who were able to spend the majority of their treatment period at home, and in two cases, return to work for short periods. These results indicate that oral idarubicin used as a single agent, despite a wide individual variation in bioavailability (Gillies *et al.*, 1987), can be useful in the palliative management of AML and CML in accelerated phase or blast crisis.

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