IMPROVEMENT IN TREATMENT FOR CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKAEMIA

The Medical Research Council UKALL Trials, 1972–84

*Report to the Council by the Working Party on Leukaemia in Childhood**

Summary Analysis of the results of United Kingdom Acute Lymphoblastic Leukaemia (UKALL) trials since 1972 showed that no improvement in remission or survival had been achieved over the 7 years up to 1979 for 1470 patients in trials UKALL II to VI. UKALL VII (1979–80) gave somewhat better results for a small group of good-prognosis patients. However, UKALL VIII, introduced in 1980, produced a 15–20% increase in 4-year disease-free survival compared with the best results of previous studies, despite a higher frequency of treatment-induced morbidity and mortality. Factors possibly contributing to this highly significant difference include the policy of continuing therapy without interruption during induction, a long course of intramuscular asparaginase over 3 weeks, full-dose mercaptopurine and co-trimoxazole during central-nervous-system prophylaxis, and the use of sustained maximum tolerated oral doses of mercaptopurine and methotrexate maintenance. An intensive sustained approach to chemotherapy in childhood ALL is needed, especially in the early stages of treatment.

Introduction

OVER the past 15 years the Medical Research Council's working party on childhood leukaemia has conducted a series of therapeutic trials in acute lymphoblastic leukaemia (ALL). The broad principles of treatment, including early prophylaxis against central-nervous-system leukaemia and long-term maintenance chemotherapy, had been established and generally accepted by 1972, and in most subsequent trials the effects of varying different aspects of this basic protocol were tested. The results were for the most part disappointing, however, and in the United Kingdom and Ireland between 1972 and 1979 there was little or no improvement in long-term remission rates.

Towards the end of that period, preliminary reports of studies being conducted by groups in the USA and West Germany suggested that they were achieving significantly higher sustained remission rates than those in the UK,[1,2] although the treatment protocols used were superficially similar. In 1980 the MRC therefore sought permission to adopt a protocol developed by the US Children's Cancer Study Group (USCCSG).[3]

This report compares the initial findings from that study, UKALL VIII, with those of earlier MRC trials.

*AUTHORS OF THE REPORT: Prof J. Peto (Institute of Cancer Research, London); Dr O. B. Eden (Royal Hospital for Sick Children, Edinburgh); Dr J. Lilleyman (Sheffield Children's Hospital); and Dr S. Richards (Clinical Trials Service Unit, Radcliffe Infirmary, Oxford).

MEMBERS OF THE WORKING PARTY: Prof R. M. Hardisty (Chairman); Dr C. C. Bailey; Dr F. Barbor; Dr N. D. Barnes; Dr C. Barton; Dr S. C. Cartwright; Dr A. W Craft; Dr J. M. Chessells; Dr S. I. Dempsey; Dr J. H. Durrant; Dr O. B. Eden; Dr P. Emerson, Prof J. J Fennelly; Prof D. A. G. Galton; Dr I. M. Hann; Dr F. G. H. Hill, Dr J. Kernahan; Dr J. S. Lilleyman; Prof T. J. McElwain; Dr J. R. Mann; Dr J. Martin; Dr P. H. Morris Jones; Dr A. Oakhill; Prof J. Peto; Dr M. Radford; Dr J. K. H Rees, Dr S. Richards; Dr R. F. Stevens; Dr G. P. Summerfield; Dr E. N. Thompson.

TABLE I—MRC TRIALS IN CHILDHOOD ALL 1972–84

Trial	Period	Eligible patients	No of eligible* patients aged 1–13
UKALL II Ordinary	1972	All patients	205
UKALL II Modified	1973	All patients	89
UKALL III Ordinary	1973–74	Low-risk†	136
UKALL III Modified	1975	Low-risk†	110
UKALL III Intensive	1973–74	High-risk†	70
UKALL IV	1975–78	High-risk†	167
UKALL V	1976–79	Low-risk†	524
UKALL VI	1978–80	High-risk†	169
UKALL VII	1979–80	Low-risk†	83
UKALL VIII Study + Trial	1980–84	All patients	805
TOTAL	1972–84	..	2358

*All eligible patients in single-arm studies (UKALL II Modified, UKALL II Intensive, and UKALL VIII Study). All eligible patients randomised at entr in other trials.

†Low-risk: WBC up to 20×10^9/litre and aged under 14. High-risk: WBC ove 20×10^9/litre and/or aged 14 or over.

Patients and Methods

The entry criteria and numbers of eligible patients aged 1 to 1 inclusive entered to the trials considered in this report ar summarised in table I.

The proportion of older patients varied between trials, in som trials adults were included, and patients aged over 14 entere between 1973 and 1979 were allocated to separate (high risk studies. To simplify the comparison of different trials the presen report is therefore restricted to patients aged 1 to 13 inclusive a diagnosis. All analyses are restricted to eligible patients randomise at notification except in UKALL II Modified, UKALL II Intensive, and the initial period of UKALL VIII (UKALL VII Study), in which all patients were allocated to a single protocol.

The UKALL VIII protocol is shown in fig 1, and protocols of th earlier trials are summarised in table II. UKALL VIII began in 198 initially as a single-arm study (UKALL VIII Study) along the line of arm 1A of USCCSG protocol 162[3] with 3 years' treatment. Fro 1982 onwards, patients were randomised to receive or not two dose of daunorubicin on days 1 and 2 and to stop maintenance after years or continue for a third year (UKALL VIII Trial). The trial wa closed to entry in December, 1984. The only substantial difference between this and previous UKALL trials were (i) intramuscula (rather than intravenous) asparaginase injections beginning on da 4 for 9 injections over 3 weeks; (ii) administration of dail mercaptopurine at full dose through the latter part of the remissio induction period without a break (during CNS prophylaxis); an

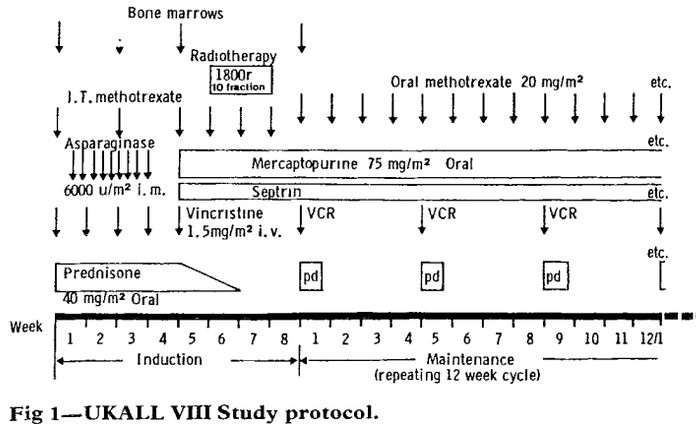

Fig 1—UKALL VIII Study protocol.

Treatment was similar in the subsequent UKALL VIII Trial except for th randomised addition of two doses of daunorubicin on days 1 and 2

TABLE II—STANDARD AND NON-STANDARD PROTOCOLS

Trial (Ref)	Standard treatment	Non-standard treatment
UKALL II Ordinary (5)	No cyclophosphamide in maintenance	Cyclophosphamide in maintenance
UKALL II Modified (5)	..	All patients received cyclophosphamide in maintenance
UKALL III Ordinary (6)	All patients, including those receiving L-Asp and/or cytarabine in maintenance	..
UKALL III Modified (6)	All patients, irrespective of "gaps" in maintenance	..
UKALL III Intensive*	..	All patients received intensive multi-drug treatment
UKALL IV*	No additional drugs in induction or maintenance	Additional drugs in induction and/or intensive intermittent maintenance
UKALL V*	Continuous or "gaps" maintenance	Intensive intermittent maintenance
UKALL VI*	All patients, irrespective of consolidation	..
UKALL VII (7)	All patients, irrespective of variations in dose, fractionation, route of administration, and testicular radiotherapy	..

*Protocols not previously published:

UKALL III Intensive.—All patients received intensive maintenance including vincristine, prednisone, methotrexate, 6-mercaptopurine, cyclophosphamide, cytarabine, adriamycin, and L-asparaginase.

UKALL IV.—Randomised addition of cyclophosphamide and cytarabine in induction, and either conventional maintenance or intermittent intensive maintenance including cyclophosphamide, adriamycin, and extra cytarabine.

UKALL V.—Randomised maintenance: continuous methotrexate and 6-mercaptopurine; a 1-week gap every 3 weeks in the 6-mercaptopurine; or both drugs given in a 5-day course once every 3 weeks. Similar total doses on all three regimens.

UKALL VI.—Randomised consolidation (weeks 4–10): either cyclophosphamide, cytarabine, and adriamycin, or high-dose methotrexate with folinic acid.

(iii) subsequent titration of the dosage of mercaptopurine and of weekly oral methotrexate according to specified levels of the neutrophil and platelet counts during remission maintenance. The principle of the trial was to start these drugs at full dosage and reduce them only in response to significant depression of neutrophil or platelet counts. During maintenance, monthly vincristine and prednisolone were given irrespective of peripheral-blood counts. After the first 6 months co-trimoxazole was introduced from week 5 of the protocol for 6 months because of a high initial frequency of interstitial pneumonitis.

Actuarial survival curves and significance levels were calculated by standard methods,[4] and randomised treatment comparisons within trials were based on allocated treatment. The relevant randomisations were allocated at entry, although in several trials the randomisation did not affect treatment until the beginning of maintenance (approximately 12 weeks after entry), and in UKALL II cyclophosphamide was not given until about week 22.

Protocol differences that were ignored in determining eligibility and in combining the trials (see table II) include the form of CNS prophylaxis (which was usually non-randomised) and duration of treatment (which was 2 years for all patients in UKALL IV and VI and was randomised, with some exceptions, to 2 or 3 years in all other trials). All analyses are based on follow-up to the end of 1984.

Standard and Non-standard Regimens

Regimens in previous trials were divided into "standard" and "non-standard" groups for the purpose of comparing their results against those of UKALL VIII. All trials except UKALL II Modified and UKALL III Intensive included a "standard" treatment arm with at least 3 weeks' conventional remission induction with daily steroids and weekly vincristine, short courses of asparaginase, CNS prophylaxis, and continuous or nearly continuous maintenance in which chemotherapy was not interrupted for more than a week and cyclophosphamide was not given. "Non-standard" regimens are defined as those in which initial induction or maintenance was intermittent or cyclophosphamide was given during maintenance. This division was based on the following considerations. A reduction in disease-free survival was observed in UKALL II in patients allocated to receive intravenous cyclophosphamide during maintenance ($p = 0 \cdot 06$)[5] and in UKALL V in patients allocated to intermittent high-dose maintenance ($p < 0 \cdot 05$). In UKALL IV both intermittent high-dose maintenance, which included intravenous cyclophosphamide, and the addition of cyclophosphamide and cytarabine during induction gave inferior results, and disease-free survival was significantly worse in patients who received either or both than in those who received neither ($p < 0 \cdot 01$). Aspects of therapy that have not produced striking differences in outcome in any trial were ignored in the analysis. These include the effects of cytarabine and L-asparaginase given in maintenance[6] and various differences in chemotherapy between the 4th and 10th weeks of treatment. The bias that such post-hoc selection may have introduced could exaggerate the overall difference between standard and non-standard treatment, but since the results of non-standard treatment were in every trial either similar to or worse than those of standard treatment it would also tend to improve the overall results of standard treatment. The main purpose of this review is to determine whether the results of UKALL VIII were better than those achieved with the best standard treatment in earlier trials.

Treatment Differences in UKALL II to UKALL VII

Mantel-Haenszel risk ratios and associated significance levels comparing patients allocated to non-standard regimens against patients allocated to standard treatment in the same trial are shown in table III. There were differences in disease-free survival between standard and non-standard regimens in UKALL II, UKALL IV, and UKALL V, but no other clear differences between randomised treatments emerged in any trial. Disease-free survival was thus highest in patients allocated to standard protocols and lowest among those allocated to non-standard protocols.

Disease-free survival in patients receiving standard treatment in different trials is compared in two ranges of

TABLE III—DISEASE-FREE SURVIVAL OF PATIENTS AGED 1 TO 13 IN UKALL II TO UKALL VII*

Trial	Allocated treatment: Standard N	Standard O	Standard E	Non-standard N	Non-standard O	Non-standard E	Significance level
UKALL II Ordinary	105	59	69·5	100	71	60·5	$p = 0 \cdot 06$
UKALL II Modified†	..	..	..	89	60	..	
UKALL III Ordinary	136	78	..	..	..	..	
UKALL III Modified	110	63	.	..	..	..	
UKALL III Intensive†	..	..	..	70	61	..	
UKALL IV	38	23	36·8	129	108	94·2	$p < 0 \cdot 01$
UKALL V	348	185	205·0	176	118	98·0	$p < 0 \cdot 05$
UKALL VI	169	112	..	..	..	..	
UKALL VII	83	32	..	..	..	.	

*Nos of patients (N) and Mantel-Haenszel observed (O) and expected (E) nos of first events (relapse or death) comparing standard and non-standard treatment.

†All patients were allocated to a single regimen in UKALL II Modified and UKALL III Intensive. Other trials for which only numbers of patients (N) and first events (O) are shown were randomised but did not include a non-standard treatment arm.

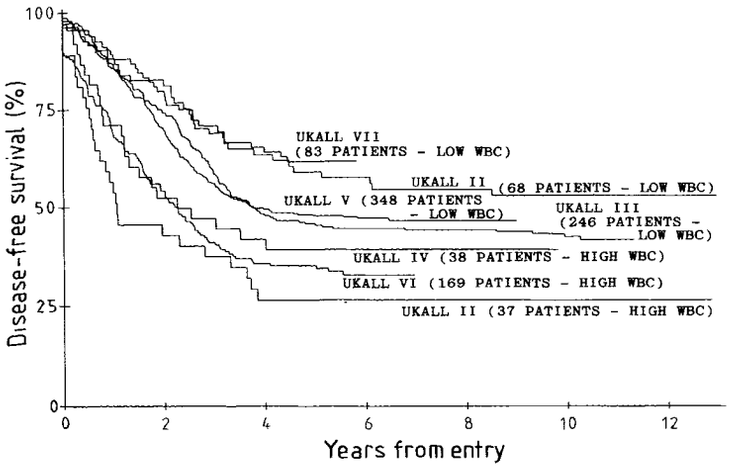

Fig 2—Disease-free survival of patients receiving "standard" treatment (see text) in successive UKALL trials, divided into low (up to 20 × 10^9/litre) and high (over 20 × 10^9/litre) WBC.

initial white-cell count (WBC ⩽ and >20× 10^9/litre) in fig 2. The only significant difference (after stratifying on WBC) is between UKALL VII and low-WBC patients in earlier trials ($p<0.05$). None of the four randomised comparisons in UKALL VII (asparaginase fractionation during induction; intrathecal methotrexate during maintenance; oral or intramuscular methotrexate during maintenance; and testicular radiotherapy) showed a statistically significant effect on disease-free survival, but the trial was small, and one or more of these treatment innovations may well have been effective.[7] The initial results of UKALL II for low-WBC patients were similar to those of UKALL VII, but there were several late relapses, and high-WBC patients in UKALL II suffered a particularly high relapse rate.

Comparison of Earlier Trials with UKALL VIII Study and Trial

In the UKALL VIII Study, which began in 1980, all patients were treated on a protocol identical to that developed by the CCSG for "average risk" patients.[3] A similar protocol with the randomised addition of daunorubicin during induction (the UKALL VIII Trial) was introduced in 1982. The combined results of Study and Trial, both of which will be described in detail in a separate report, are compared in figs 3a, 3b, and 3c against the combined results of standard and non-standard treatment in earlier trials in three ranges of WBC (⩽20, 20–50, and >50× 10^9/litre). The relapse rate has been consistently lower in UKALL VIII than in any previous trial, and the disease-free survival rate at 4 years is 15–20% higher in each WBC range than the results previously achieved with standard treatment. Even in UKALL VII, which achieved better results than any previous trial, disease-free survival was lower than in UKALL VIII. Longer follow-up will be needed before the long-term disease-free survival rate can be predicted accurately, but in all earlier trials the relapse rate has been low beyond 4 years, and if the same pattern occurs in UKALL VIII the proportion of patients achieving long remission seems likely to be almost 50% among children with WBC exceeding 50× 10^9/litre, and about 65% in those with WBC under 20× 10^9/litre.

Discussion

Comparisons between different trials of cancer therapy are often of doubtful validity, because differences in referral, patient selection, and staging procedures can produce spurious differences which disappear when the same treatments are evaluated in a randomised study. For childhood ALL, however, the effects of such biases may be less pronounced. Referral of children to collaborative studies in the UK does not appear to be subject to much variation of selection criteria, since participating clinicians usually enter all their patients, and the validity of our comparisons between different trials is further supported by the observation that similar treatments in successive trials gave similar results, and that the UKALL VIII results are similar to those of the identical and concurrent USCCSG 162 schedule in the USA (J. N. Lukens, personal communication). We therefore believe that the striking therapeutic improvement which appears to have been achieved in UKALL VIII is real.

At the time when UKALL VIII was being planned, results from the USA[1] and West Germany[2] appeared to be so much

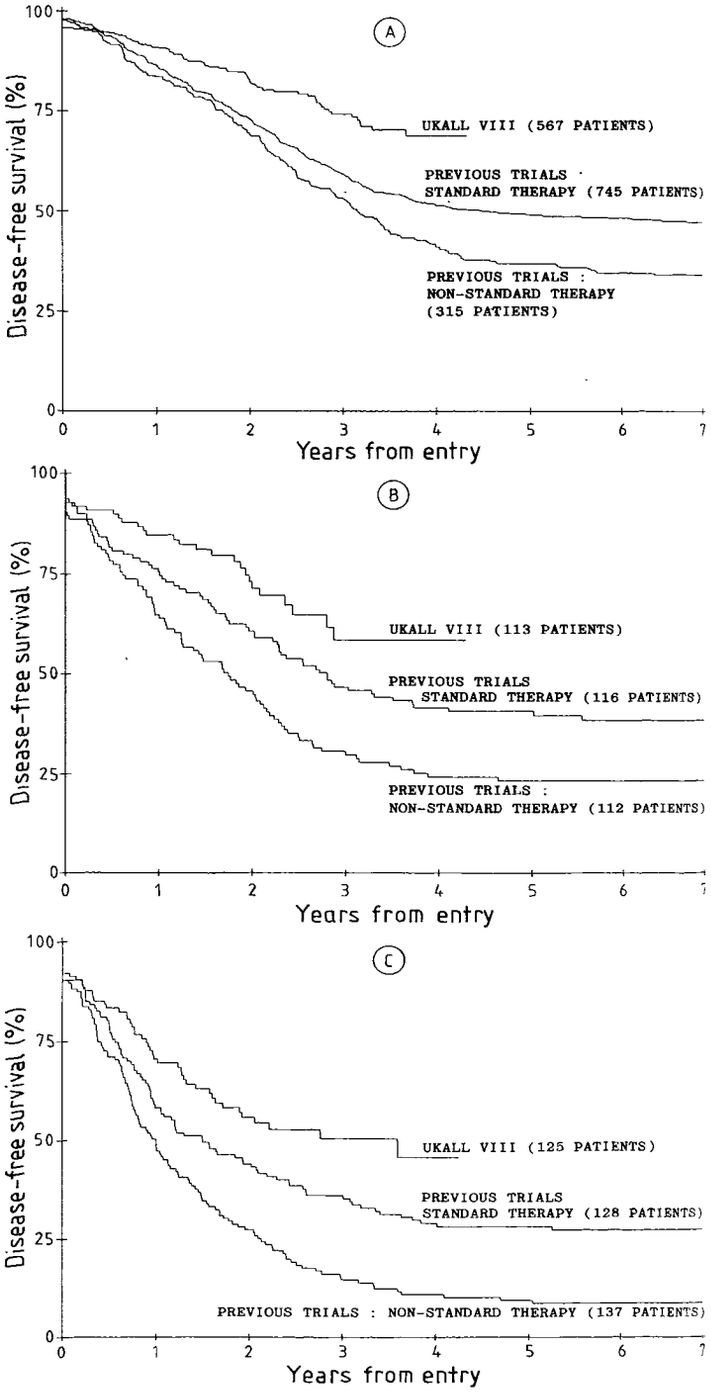

Fig 3—Disease-free survival, in UKALL II to VII combined, of patients receiving "standard" or "non-standard" treatment (see text) compared with UKALL VIII (Study and Trial combined).

Results are shown separately for WBC (a) up to 20× 10^9/litre (b) 20 to 50× 10^9/litre and (c) over 50× 10^9/litre.

better than those of earlier UKALL trials that it was thought to be ethically unacceptable to include control groups in which different aspects of the differences in treatment between UKALL VIII and earlier trials were randomised. This decision appears to have been correct in view of the improvement that has occurred, but the penalty that we have paid is substantial. Apart from the possibility of bias that only a randomised study can avoid, we can only speculate on the importance of different aspects of therapy. The simplest and most plausible interpretation is that insistence on the use of anti-leukaemic agents at maximum dosage increases the probability of cure, but we do not know that this is true for all drugs or whether it is equally important during remission induction and during maintenance. The administration of asparaginase early in treatment rather than after a few weeks and for a longer period, which is the only other specific difference between UKALL VIII and earlier protocols, may be crucial or irrelevant.

It seems paradoxical that every previous attempt to increase the intensity of treatment led to inferior results, for the major difference between UKALL VIII and previous studies appears to be the maintenance of maximum dosage throughout treatment in UKALL VIII. One possible explanation is that the addition of cyclophosphamide or other agents in previous trials entailed a reduction or interruption of standard chemotherapy. This is supported by our observation in both UKALL IV and UKALL V that intermittent maintenance is inferior to continuous treatment, and the most striking clinical difference between UKALL VIII and earlier trials is sustained myelosuppression during maintenance in UKALL VIII.

Further refinements in treatment will inevitably be difficult to achieve. Long-remission rates are now high, particularly among patients with a good prognosis, and clinicians will be reluctant to experiment with radically different treatments. The most practicable course is to increase the intensity of treatment during selected periods in randomised studies, and this is being done in the current UKALL X study. This seems ethically acceptable, since it is not clear whether the risks that must accompany more intensive early treatment or the prolonged myelosuppression commonly found throughout maintenance in UKALL VIII will be outweighed by further reductions in the risk of recurrence.

Correspondence should be addressed to Prof J. Peto, Institute of Cancer Research, Royal Marsden Hospital, Sutton, Surrey SM2 5PX.

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FREQUENCY OF SEVERE NEUTROPENIA ASSOCIATED WITH AMODIAQUINE PROPHYLAXIS AGAINST MALARIA

C. S. R. HATTON C. BUNCH T. E. A. PETO G. PASVOL

Nuffield Department of Clinical Medicine and Tropical Medicine Unit, University of Oxford, John Radcliffe Hospital, Headington, Oxford OX3 9DU

S. J. RUSSELL C. R. J. SINGER

Department of Haematology, University College Hospital, London

G. EDWARDS P. WINSTANLEY

Department of Pharmacology and Therapeutics, University of Liverpool, Liverpool

Summary 6 out of 7 patients with severe neutropenia associated with the use of amodiaquine for malaria prophylaxis amodiaquine (400 mg weekly) plus proguanil (200 mg daily); 1 of these patients had also taken co-trimoxazole and another had taken sulphaguanidine. The 7th patient had taken amodiaquine alone, but at a higher dose. A retrospective analysis suggests that the frequency of severe neutropenia complicating amodiaquine taken prophylactically may be as high as 1 in 2000.

Introduction

THE emergence of chloroquine-resistant strains of *Plasmodium falciparum* has made malaria prophylaxis for travellers to endemic areas difficult. A further difficulty is that existing anti-malaria agents produce side-effects. Following reports of severe agranulocytosis associated with the use of pyrimethamine and dapsone in combination ('Maloprim'), the policy at the Tropical Medicine Unit in Oxford was changed in 1984 so that a combination of amodiaquine and proguanil became the recommendation for travellers to chloroquine-resistant areas. Amodiaquine is more effective than its close analogue chloroquine, both for treatment and prophylaxis, in some chloroquine-resistant areas.[1] Furthermore, although neutropenia has been associated with amodiaquine,[2–13] it is generally considered to be a rare complication.[14] However, in the past 12 months we have seen seven cases of this complication, 6 in Oxford and 1 (patient 6) in London.

Case-reports (Table)

Patient 1

On his return from a 6-week visit to West Africa a 51-year-old scientist was admitted to hospital with a 10-day history of sore throat, headaches, and fevers. He had taken amodiaquine 400 mg weekly and proguanil 200 mg daily throughout his stay in Africa and until his admission to hospital in Oxford. In Chad he had received a 4-day course of co-trimoxazole, paracetamol, and histapyrrodine.

His temperature was 38°C; pulse 110/min, and blood pressure 110/80 mm Hg. He was jaundiced, and had an indurated erythematous area over his left flank. His haemoglobin (Hb) was 12·5 g/dl, leucocytes $0{\cdot}6\times10^9$/l, and platelets 290×10^9/l; no neutrophils or malaria parasites were seen on the blood film. Bone-marrow examination 3 days after admission showed no granulocytes beyond the myelocyte stage. He was given intravenous netilmicin and piperacillin. After a stormy course, which included the development of a large axillary abscess, he recovered and was sent home 4 weeks later with Hb 14·0 g/dl, leucocytes $7{\cdot}8\times10^9$/l (70% neutrophils), and platelets 451×10^9/l.