ACUTE HAEMORRHAGIC PANCREATITIS FOLLOWING L-ASPARAGINASE THERAPY IN ACUTE LYMPHOBLASTIC LEUKAEMIA —A CASE REPORT

By C. L. Tan, S. P. Chiang and K. P. Wee

SYNOPSIS

A fatal case of acute haemorrhagic pancreatitis following L-asparaginase therapy in a boy with acute lymphoblastic leukaemia is reported. The toxicity of the drug is briefly reviewed, emphasing anaphylactic shock and acute pancreatitis as being potentially life-threatening. A stand is made to justify further cautious trials using combination chemotherapy, including L-asparaginase, for cases of acute lymphoblastic leukaemia, in view of disappointing results with conventional therapy.

INTRODUCTION

Throughout the world there has been a gradual change of attitude through the years towards the treatment of acute leukaemia. From therapeutic nihilism we then entered the era of palliative chemotherapy, the aim being to prolong the life of the patient with the hope that further significant therapeutic advances would be discovered before the inevitable relapse and death of the patient. It is probably true to say that we in Singapore have had to be content to remain at this stage for many years. However the world is now entering the radical era where the aim is that of total cure—at least in a small percentage of leukaemia patients—by destroying every leukaemic cell in the patient's body (Hardisty 1970). To achieve this goal, various schemes of drug usage for induction, consolidation, intensification, reinduction and maintenance have been tried and already some have been shown to give projected median survivals by life table analysis in excess of 30 months (George *et al*, 1968 and Henderson, 1967) and even up to 60 months (Aur, 1971 and Pinkel, 1971). The role of immunotherapy too has been given prominence by certain authors (Mathe, 1971 and Crowther *et al*, 1973), though a preliminary report to the Medical Research Council by the Leukaemia Committee and the Working Party on leukaemia in childhood (1971) appears to cast doubt on the value of immunotherapy with B.C.G.

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An analysis of cases of acute lymphoblastic leukaemia (ALL) admitted to Paediatric Unit (East) from 1967 to 1972 showed that in each year from 1967 to 1970, the average length of survival from the time of diagnosis was only about 7 months. The corresponding figure for cases in 1971 is more encouraging, being 17 months with 2 of the 9 patients that year still alive. A combination of vincristine and prednisolone is currently the accepted orthodox method for the initial induction of remission in cases of ALL. Of the 33 cases of ALL from 1967-1972, this treatment was used in 9 patients, being first used in 1970.

Apart from the superior results shown with intensive combination chemotherapy schemes, there have also been reports showing that maintenance with intermittent high dosage methotrexate (MTX) gives better results than daily MTX (Acute Leukaemia Group B, 1965 and Holland *et al*, 1970). Also prophylactic intrathecal MTX has been shown to protect some 85% of patients from developing central nervous system (CNS) leukaemia over a 30-month period, whereas 50% who did not receive this therapy developed this complication (Sinks, 1972). Cranial irradiation plus intrathecal methotrexate gives equally good, if not better results (Aur, 1971 and Leukaemia Committee, 1973).

Since 1973 these regimes have been incorporated into our protocol wherever possible, though for several reasons, our intensive combination chemotherapy scheme has had to be a modified one. Our case report is in fact the first patient who was put onto the scheme, and it is unfortunate that he succumbed not to leukaemia but to an unexpected complication of chemotherapy. The aim of our paper is to draw attention to an uncommon but potentially fatal complication of L-asparaginase (L-APG) therapy and to briefly review its other toxicities.

CASE REPORT

L.S.C., a Chinese boy, was first admitted to Paediatric (East) Unit on 26.1.73 at the age of 4 years 3 months, with the history of progressive pallor, anorexia and weight loss for the preceding 3 months. There was no history of a bleeding tendency or of the child having been X-rayed in utero or at any time since birth. Birth history and developmental milestones were normal. Another sibling, a girl aged 3 years, was well. There was no history of any blood disorder in the family.

On examination, his general condition was satisfactory. He was pale with a few small purpuric patches on his legs and a few petechiae on the buccal mucosa. The fundi were normal. The liver was enlarged to 2 cm. below the right costal margin and the spleen 1 cm. below the left costal margin. He had generalised lymphadenopathy. Other systems were normal.

The blood counts on admission were as follows:—

Hb 5·3 Gm.% WBC 3,100/c.mm. Polymorphs 16% Lymphocytic 80% Monocytes 2% Eosinophits 2% Platelets 15,000/c.mm.
Blast cells occasional
Peripheral blood film: mixed picture
Reticulocyte count: <1% E.S.R.: 124 mm.

A provisional diagnosis of acute lymphoblastic leukaemia was made and he was started on prednisolone 40 mg./m.^{2} and given blood.

Repeated marrow punctures produced a dry tap over the next 3 days and weekly intravenous vincristine 2 mg./m.^{2} was only started from 31.1.73 when the bone marrow finally confirmed the diagnosis of acute lymphoblastic leukaemia.

He responded well to treatment, the blood counts returning to normal after 3 weeks. However, a bone marrow done after 4 doses of vincristine still showed incomplete remission and it was only after the 6th dose of vincristine that the bone marrow done on 14.3.73 showed a complete remission (see Fig. 1: Treatment Chart of Patient). The parents had earlier consented to any intensive chemotherapy scheme that we were contemplating. Hence he became the first ALL patient to go onto our intensive chemotherapy protocol (subsequently modified— see Fig. 2). He was started on 6-mercaptopurine and given 2 doses of intrathecal MTX (10 mg./m.^{2} per dose) followed by IV asparaginase (10,000 units run in as a drip infusion with 200 cc. normal saline over 3 hours) on 23.3.73. Syringes with adrenaline and hydrocortisone were kept at his bedside during the asparaginase infusion. He tolerated the asparaginase well with no allergic reaction or fever and was discharged well on 24.3.73.

He was again admitted on 30.3.73 for the 3rd dose of intrathecal MTX and a 2nd dose of IV APG 10,000 units and discharged well the next day.

Meanwhile Prednisolone was being gradually tailed down from 27.3.73 and was taken off completely on 3.4.73 when he came as an outpatient for follow up and was found to be well and still in full haematological remission. He, however, returned the next day and was admitted in the afternoon with the history of central colicky abdominal pain starting since 7.30 a.m. the same day. The pain did not radiate and there was no vomiting. There had been a past history of vague abdominal pain before his illness.

On examination, his general condition was satisfactory. He had a Cushingoid appearance. His extremities were warm and he was not in shock. His blood pressure was 110/70 mm. Hg. The abdomen was soft with no local tenderness. The liver edge was palpable 2 cm. below the right costal margin. The spleen was not palpable and no masses were felt. Other systems were normal. It was thought that he might be having gastritis and he was put on antacids. He was also given an injection of 20 units ACTH. He continued to complain of colicky abdominal pain and was later given an atropine injection without much effect. The abdomen remained soft and non-tender on palpation and a surgical condition was not entertained. The blood counts were unremarkable, viz. Hb 10·2 Gm.%, WBC 4,800/c.mm. Platelets 190,000/c.mm. No blasts cells were seen. However, about 18 hours after admission he was noticed to be cold and clammy with a rapid thready pulse of about 140/minute. The blood pressure was 90/50 mm. Hg. The abdomen remained soft and non-guarded. An intravenous drip was set up. However, the patient suddenly collapsed and died soon after, despite resuscitative measures.

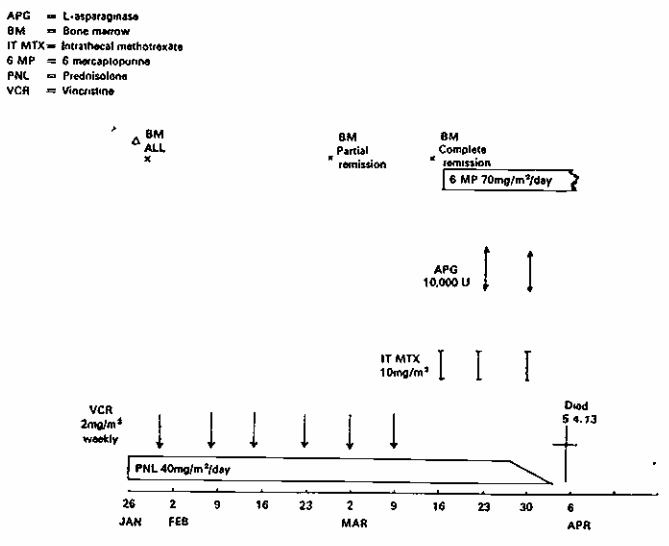

FIG. 1. TREATMENT CHART OF PATIENT.

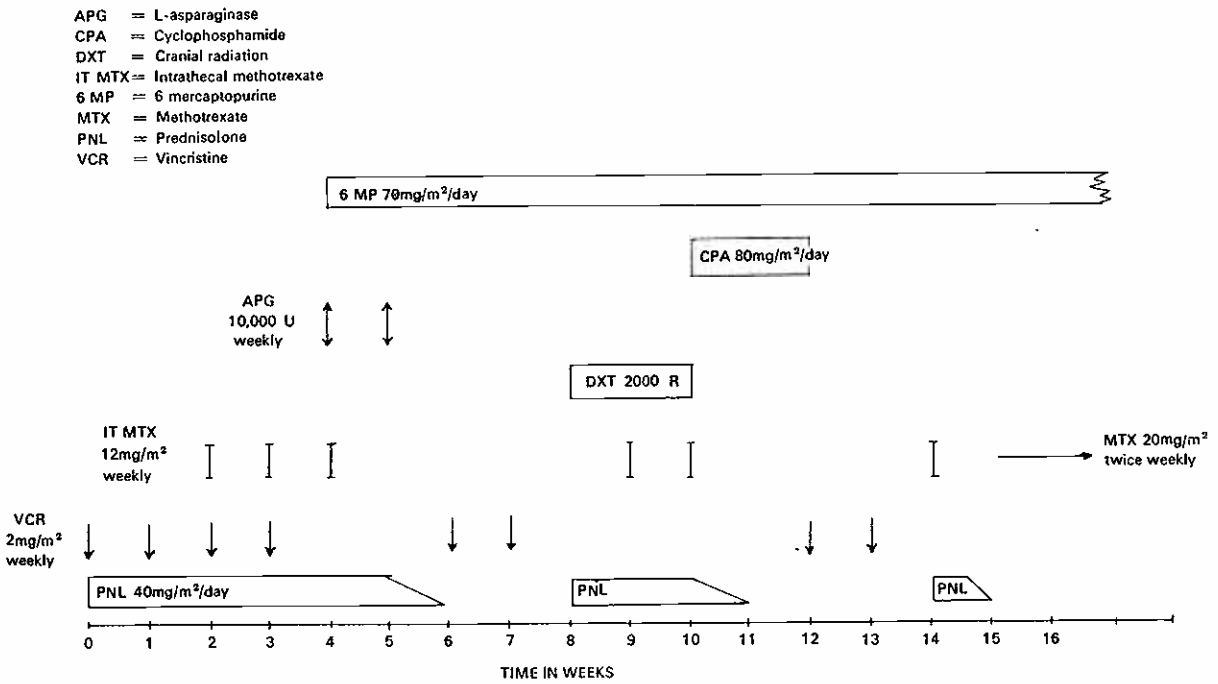

Fig. 2. COMBINATION CHEMOTHERAPY SCHEME FOR ACUTE LYMPHOBLASTIC LEUKAEMIA

POST-MORTEM EXAMINATION

The post-mortem was performed 31 hours after death.

Gross Findings

The body was that of a male child with Cushingoid facies, size consistent with age: height of 101 cms. and weight 16·10 Kgs.

Externally, there was no evidence of a bleeding tendency or of lymphadenopathy. The gums were normal. A full post-mortem was performed. The body cavities were normal, with no evidence of ascites or effusions.

The main findings were in the abdomen.

The pancreas was grossly enlarged and diffusely haemorrhagic. The biliary system was explored and no abnormality was detected. The sphincter of Oddi appeared oedematous. No calculus was detected.

The liver was enlarged to about 1½ times its normal size, weighing 678 gms. There was gross evidence of fatty change.

Patchy serosal ecchymoses were noted in the descending colon. There was no evidence of infarction or of intestinal obstruction. The rest of the alimentary tract was normal.

Microscopic Findings

The main histological features were found in the pancreas (Fig. 3). Sections showed extensive haemorrhagic necroses of pancreatic acini with destruction of the pancreatic architectural pattern. There was severe interstitial oedema with a heavy infiltrate of polymorphonuclear leucocytes. Venous thromboses were seen. There was no evidence of calcification. These changes were consistent with that of an acute haemorrhagic pancreatitis.

Microscopically, the liver confirmed the gross features of fatty change. The distribution was mainly perilobular. There was no evidence of cirrhosis. The portal tracts and central veins appeared normal.

DISCUSSION

The post-mortem findings clearly show that our patient died not from ALL but from acute haemorrhagic pancreatitis, almost certainly the result of L-asparaginase therapy.

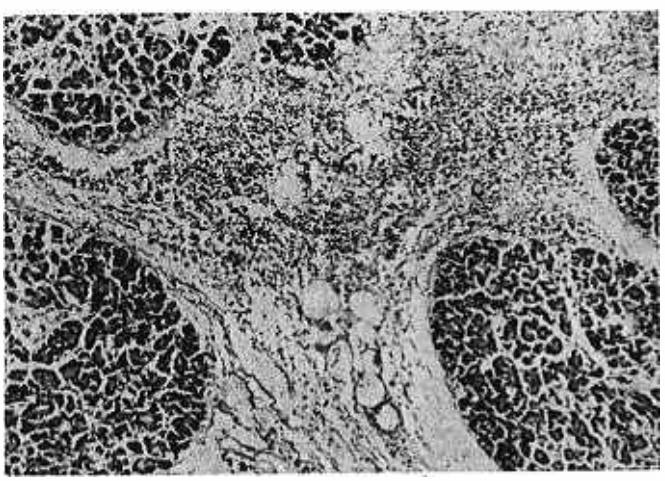

Fig. 3. H & E 75 × Picture shows severe interstitial oedema, a heavy infiltrate of polymorphs and accompanying haemorrhagic necrosis of the pancreas.

L-asparaginase, an enzyme that makes exogenous L-asparagine unavailable to cells, was incorporated into our combination chemotherapy scheme mainly because it is of proven value in the treatment of ALL and it is relatively harmless to normal bone marrow cells, being selectively toxic to leukaemic cells which are killed. (Ho *et al*, 1970). Thus its use need not be curtailed in the face of marrow aplasia arising from any intensive chemotherapy scheme (Colebatch *et al*, 1970).

In fact, when first publications showed that L-asparaginase could induce complete remission in about 50% of patients with ALL (Oettgen *et al*, 1967; Hill *et al*, 1967), the excitement generated was greater than that for any other anti-tumour drug. It was initially thought that L-asparaginase was the first anti-tumour drug which killed the invading cells without harming the host, and that its anti-leukaemic effects in man could be predicted by an in vitro test. Both theories have been disproved in practice (de Vaan *et al*, 1971). In fact more and more unexpected toxicities of L-asparaginase have emerged with its wider use.

Dosage has ranged from 200-5000 IU/Kg./day or from 7000-20,000 IU/m.^{2}/week for 4-5 weeks for children with acute leukaemia. It would appear that the lower dosage is more than adequate (Zubrod, 1970).

The commoner side effects of L-asparaginase are fever, nausea, vomiting and anorexia (Haskell *et al*, 1969b). Fever is probably due to the fact that most preparations of L-asparaginase are not completely free of contaminating endotoxin and other bacterial products.

The other side effects can be grouped under five headings, viz. hypersensitivity reactions, derangement of liver function (Haskell *et al*, 1969 a + b; Land *et al*, 1970) coagulation defects (Haskell *et al*, 1969b and Gralnick *et al*, 1969), central nervous system effects such as disorientation, convulsions and coma, and pancreatic dysfunctions manifested by pancreatitis, hyperglycaemia or glycosuria, ketoacidosis or ketonuria. Of all these side effects, anaphylactic shock and acute pancreatitis stand out as being potentially life-threatening.

Of the hypersensitive reactions, urticaria is fairly common. Anaphylactic shock unfortunately is not that rare. In Haskell's series there were 14 instances of hypersensitivity, mostly urticaria, out of 55 patients treated. However 2 patients had non-fatal anaphylactic shock. In the Colebatch series, there were 2 cases of anaphylactic shock, both non-fatal out of 15 cases given L-asparaginase. Fatality from anaphylactic shock fortunately is uncommon, there having been 2 deaths reported to the National Cancer Institute from about 300 patients treated (Zubrod, 1970). It would appear that skin testing is of no value in predicting hypersensitivity to L-asparaginase (Land, 1972 and Zubrod, 1970). Careful observation of a patient during an intravenous drip infusion of the drug, with syringes containing adrenaline and hydrocortisone by the bedside is the best policy, and this was done in our case.

The most dangerous complication of L-asparaginase therapy is acute haemorrhagic pancreatitis which presents with abdominal pain going on to shock. High serum amylase values may be found. Land (1972) however found the serum amylase to be a poor guide in predicting pancreatitis. Of the 4 deaths due to haemorrhagic pancreatitis out of 105 patients on L-asparaginase, in only one was the serum amylase level raised. Two further patients with mild pancreatitis on post-mortem examination also had normal levels. Serum amylase was not estimated in our patient.

There were 4 deaths due to pancreatitis reported to the National Cancer Institute from 300 patients who had received L-asparaginase (Zubrod, 1970). A 10% incidence of less fulminating and non-fatal pancreatitis has also been reported (Haskell *et al*, 1969b and Whitecar *et al*, 1970a). Transient hyperglycaemia, glycosuria and ketoacidosis can occur. In Land's (1972) series, one patient died with diabetic ketoacidosis. It has been shown that L-asparaginase inhibits insulin synthesis (Whitecar *et al*, 1970b).

It should be noted that pancreatitis associated with corticosteroid therapy has been reported (Anderson *et al*, 1961, Nelp *et al*, 1961 and Oppenheimer *et al*, 1960) as being associated with pancreatic epithelial proliferation, inspissated secretions, and dilated and atrophic acini, probably secondary to an increased quantity and viscosity of pancreatic secretions. Land (1972) noted that in 3 of the 4 cases of fatal heamorrhagic pancreatitis, prednisone was also being administered at the time of death. Their histology however, showed diffuse haemorrhagic necrosis with no evidence of ductal dilation or inspissated secretions, and the authors concluded that the addition of prednisone bore no relationship to the occurrence of pancreatitis in their study. We can conclude likewise on histology.

Both anaphylactic shock and acute haemorrhagic pancreatitis tend not to occur with the first dose of L-asparaginase but after repeated injections. It has also been recommended that toxic manifestations may be decreased by giving the drug weekly over a two week period instead of daily. Prolongation of treatment beyond two weeks is not indicated because of the promptness of response by sensitive

cells and the potential toxicity of the agent (Pratt, 1970). Thus one should be fully prepared to deal with anaphylactic shock with each dose of L-asparaginase. The diagnosis of pancreatitis however is more problematic due to its poor correlation with a rise in serum amylase level. Treating every child who complains of abdominal pain with or without vomiting while on L-asparaginase, as a potential case of pancreatitis (even though abdominal palpation shows no guarding or tenderness) by monitoring the patient for shock and giving early intravenous fluid therapy (especially plasma for hypotension) would be a rational approach. In fact the striking disparity between the severity of pain and the paucity of abdominal signs should make one suspect the diagnosis even before the clinical picture changes after a few hours to classically simulate a perforated peptic ulcer with guarding and rigidity of the abdominal wall (Trapnell, 1968). Our case certainly re-emphasizes the importance of knowing all the side effects of drugs used, especially potentially dangerous drugs, and of knowing them well.

In conclusion, L-asparaginase still remains a valuable addition to the therapy of ALL in spite of its toxicity. Its priority in the therapeutic armamentarium however is yet to be clearly defined, but enough is known of the drug to justify its continued inclusion in trials aimed at achieving a therapeutic breakthrough in as serious a disease as acute leukaemia.

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