Treatment of Acute Lymphoblastic Leukaemia

Joe DeGiovanni and Robert Carachi

Case history: P.T. was an 8 year old child complaining of lassitude, tiredness, anorexia and loss of weight. Admitted on 2/4/69.
Past history: Chicken pox, mumps and measles.
Family history: Nothing relevant.

On examination the patient was anaemic, and had scattered non-tender glands in the axillae and small haemorrhages on the hard palate. Pulse 90 regular. JVP:O. B.P. 120/80. Soft systolic ejection murmur maximal at the apex. Chest clinically clear. Firm hepatic enlargement (2 fingers) and palpable spleen. C.N.S. : N.A.D.

Marrow punture revealed acute lymphoblastic leukemia; 50% of the cells were blasts.

Blood: Hb. 6.2 gm., platelets 206,000, WBC 4,900.

He was started on the MRC regime for acute lymphoblastic leukaemia using Prednisone, Vincristine, 6-Mercaptopurine, Methotrexate, Asparaginase and Folinic acid. These were given according to a planned pattern and stopped 21 weeks after immunotherapy by BCG was started; the BCG was given weekly and the patient has remained in remission for 2 years.

In acute leukaemia there is an accumulation of malignant colonies of abnormal blast cells in the bone marrow and other tissues resulting in poor red cell, platelet and granulocyte production and leading to a fatal result if left untreated.

Management:

Originally treatment was merely supportive together with irradiation of local infiltration. The results were very disappointing but they have been markedly improved with the introduction of Cytotoxic drugs. The best results have been obtained with Intensive Combination Drug Therapy (Fig 1.). Increasing the dose of a chemo therapeutic agent above a certain limit merely increases the toxicity without altering the remission rate. The use of a drug combination with different side effects may allow the same dose of each agent to be given with no added toxic effects.

Figure 1

	Mean survival
No specific treatment	5 Months
Folic acid antagonists + Steroids.	9 Months
Purine Antagonists	12 Months
VCR + Endoxan	14 Months
Intensive Combination therapy	Over 3 years

The use of combination therapy has not only increased the mean survival but the quality of life has also been improved considerably.

Treatment of acute leukaemia is more limited than that of solid tumours because of dissemination which rules out the use of Surgery and Radio-therapy, and so one has to resort to chemotherapy. Besides the treatment of the actual disease one has to prevent complications by giving supportive therapy such as platelet transfusion, prophylactic antibiotics, prevention of meningeal leukaemia and hyperuricaemia together with the use of Barrier Nursing.

The modern approach in the treatment of acute lymphoblastic leukaemia involves 3 steps:

1. Remission induction.
2. Cytoreduction of residual leukaemic cells.
3. Maintenance.

1. Remission induction.

Remission induction involves treatment with chemotherapy until the patient becomes clinically free from disease. This can be achieved by using Vincristine and Prednisone with a remission in 85% of cases. If this fails Daunorubicin can be added and there can be a remission in 90% of cases or else Rubidomycin and the remission occurs in 100% of cases but there is an increase in toxicity with the last two agents. Other cytotoxic drugs have been used such as L-Asparaginase, Methotrexate, 6-Mercaptopurine, Cyclophosphamide and Cytosine Arabinoside.

With remission induction one does not eradicate all the malignant cells and up to 10^9 leukaemic cells may still remain undetected.

2. Cytoreduction chemotherapy.

The number of residual leukaemic cells can be reduced to a minimum by cytoreductive chemotherapy using different drugs from those used to induce the original remission.

Continuing the chemotherapy with a single agent during periods of remission intermittently results in prolongation of remission. However, combination chemotherapy is more effective. Drugs commonly used for this purpose are Prednisone, Vincristine, Methotrexate, 6-Mercaptopurine and L-Asparaginase.

The logic behind this step is that leukaemic cells are not rapidly dividing cells as was previously thought. In some malignant diseases the cell doubling time may be even longer than normal cells. The intermittent use of antimitotic drugs enables the normal cells to recover more rapidly than malignant cells between the doses of the drug. Thus it can be given in larger doses and is more effective in prolonging remissions.

The management of the patient in complete remission and the elimination of the residual disease is the main difficulty in the treatment of acute leukaemia. The problem is further complicated by the fact that the treatment is given blindly at this time because it is not known how much leukaemic cells are still present. What

is required is a marker that can give an estimate of the amount of tumour left. The discovery of such a marker whether it be a circulating tumour antigen, enzyme, hormone or other metabolite would revolutionize the treatment of acute leukaemia.

3. Maintenance.

This can be achieved by any of these 3 methods: (i) Chemotherapy (ii) Immunotherapy (iii) Immunotherapy + Chemotherapy

Immunotherapy

This increases the resistance to tumour growth by stimulating an immunological response. Theoretically it can be achieved in various ways, but in practice only some are effective.

a) Passive immunotherapy. This consists of the administration of horse antilymphocytic serum but it has not proved to be effective; moreover, it can be dangerous because the serum has cytotoxic and enhancement antibodies and these cannot be separated.

b) Active immunotherapy. For this to be effective the number of tumour cells must be very small — less than 10^5 in the case of mouse leukaemia L1210. Active immunotherapy is only justified if the leukaemic cells carry a specific antigen. It has been found by Dore' that a third of patients with leukaemia have antibodies in their sera against their own leukaemic cells and those of other leukaemic patients; therefore, part of the resistance offered by the host against leukaemia is immunological.

Active immunotherapy can be specific or non-specific. These can be used concurrently. Specific immunotherapy consists of injecting irradiated leukaemic cells which still carry antigenic properties or by injecting the antigen directly. Non-specific immunotherapy consists in the stimulation of the lympho-reticular system by non-specific antigens such as B.C.G. With the exception of one study by Prof. Mathe' other experimenters have not come up with any good results in this field.

c) 'Adoptive' immunotherapy is based on the antileukaemic effect of the lymphocytes transfused or produced by bone marrow grafts. Remissions with transfused lymphocytes are short while with Bone Marrow grafts they can be much longer. Remissions with the latter are induced by the reactions of the lymphocytes against the leukaemic cells and correspond to a cure if all the leukaemic patients' haemopoietic tissue is destroyed. However the graft affects normal antigens and may induce a severe lethal disease, 'Secondary disease'. Because of these dangers in acute lymphoblastic leukaemia, adoptive immunotherapy must be reserved for patients refractory to chemotherapy.

Conclusion:

The case presented was one of Acute Lymphoblastic Leukaemia which has been in remission for 2 years during which period P.T. was on Non-Specific Immunotherapy by giving B.C.G. with the Multiple Puncture Technique (Heaf). Whether this long remission is due to the immunotherapy or not has yet to be proved.