ORIGINAL ARTICLES

UKALL X—an effective treatment for stage III mediastinal non-Hodgkin’s lymphoma

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Abstract
Fifteen children with mediastinal non-Hodgkin’s lymphoma were treated with MRC UKALL X, the current national protocol for acute lymphoblastic leukaemia. The treatment was well tolerated, and in a minimum follow up period of 46 months the event free survival of 93% was significantly better than that in a group of historical controls treated with intermittent chemotherapy regimens whose survival was only 57%. We conclude that intensive induction and consolidation treatment, with continued oral drugs, provides an effective approach to the management of mediastinal non-Hodgkin’s lymphoma.

Mediastinal non-Hodgkin’s lymphoma is an aggressive disease with a high risk of dissemination to the bone marrow and the central nervous system. Histological examination of the biopsy specimen of the mass or of the associated lymph nodes usually shows the features of lymphoblastic lymphoma, and immunological classification shows that nearly all these tumours have the features of immature T cells.¹ The relationship of T cell leukaemia to lymphoma is controversial, and there has been long standing debate about whether treatment should comprise an intermittent multiple drug regimen, or the type of continuous treatment that is used in acute lymphoblastic leukaemia.

We report here our experience of using the Medical Research Council United Kingdom acute lymphoblastic leukaemia (MRC UKALL)

X D protocol (one arm of the current national trial for the treatment of acute lymphoblastic leukaemia) in a group of children with mediastinal lymphoma, and compare their outcome with that of a group previously treated with intermittent regimens of several drugs.

Patients and methods
Fifteen consecutive children presenting from 1982 to 1985 were entered into the study (table). There were 11 boys and four girls and the median age at diagnosis was 6·5 years (range 1–15). The historical control group comprised 14 consecutive patients who presented between 1974 and 1981, of whom there were 10 boys and four girls with a median age of 6·5 years (range 2–13). There were no significant differences in age and sex distribution between the two groups.

The stage of the disease was established in all patients with a chest radiograph, bone marrow aspirate, and lumbar puncture, and the study patients also had an ultrasound examination of the abdomen. All the children had stage III disease according to the Murphy staging system—that is, extensive supradiaphragmatic disease without bone marrow or central nervous system disease.¹ The diagnosis (table) was determined by examination of biopsy specimens from lymph nodes in four children, from mediastinal masses in six, and by examination of pleural fluid in five. Immunological analysis of the material was carried out in 11 of the 15 cases, and in all the tumour was of T cell origin.

The historical group of patients had all

Clinical features of 15 patients treated with MRC UKALL X

Case No	Age (years)	Sex	Affected sites	Site of tissue diagnosis	Event free survival time (months from diagnosis)
1	13	Male	Mediastinum	Mediastinum	85
2	9·5	Male	Mediastinum, pleural fluid	Pleural fluid	83
3	11	Female	Mediastinum, supradiaphragmatic lymph nodes	Supradiaphragmatic lymph nodes	83
4	5	Female	Mediastinum	Mediastinum	82
5	6·5	Male	Mediastinum, pleural fluid, supradiaphragmatic lymph nodes	Pleural fluid	81
6	1	Male	Mediastinum, pleural fluid	Mediastinum	7
7	15	Male	Mediastinum	Mediastinum	64
8	2	Female	Mediastinum	Mediastinum	63
9	10	Female	Mediastinum, pleural fluid, supradiaphragmatic lymph nodes, kidney	Supradiaphragmatic lymph nodes	62
10	5	Male	Mediastinum	Mediastinum	56
11	6·5	Male	Supradiaphragmatic lymph nodes	Supradiaphragmatic lymph nodes	54
12	14	Male	Mediastinum, pleural fluid, kidney	Pleural fluid, kidney	53
13	5·5	Male	Mediastinum, pleural fluid	Pleural fluid	53
14	4	Male	Mediastinum, supradiaphragmatic lymph nodes	Supradiaphragmatic lymph nodes	49
15	5	Male	Mediastinum, pleural fluid	Pleural fluid	48

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Accepted 19 September 1989

received intermittent multiple drug regimens of repeated injections at intervals of three weeks; nine had been treated with the United Kingdom Childhood Cancer Study Group (UKCCSG) protocol, which has previously been reported.² The study patients received induction treatment with vincristine, daunorubicin, crisantaspase (L-asparaginase), prednisolone, and intrathecal methotrexate. Five received early intensification with a pilot schedule for MRC UKALL X and the rest received early and late intensification with several drugs, as previously described.³ Continuing treatment with prednisolone and vincristine every four weeks, daily 6-mercaptopurine, and weekly methotrexate, was given for two years from the time that remission was achieved. All patients received standard treatment to the central nervous system with cranial irradiation (18 Gy) and a course of intrathecal methotrexate injections.

All patients have now been followed up until June 1989, with a minimum follow up of two years without treatment. Difference in survival time between the two groups was calculated by the log rank method.⁴

Results

All 15 patients achieved remission. One child (the youngest in the series) relapsed with disease in the mediastinum seven months after diagnosis, and subsequently relapsed with disease in the central nervous system; he died one year after diagnosis. The others are all well and off treatment. The event free survival (figure) is 93% at four years, which is significantly better than that in the control group ($p=0.015$). Failures in the control group were due to one induction related death, two bone marrow relapses, two mediastinal relapses, and one relapse in the central nervous system.

Treatment was well tolerated. The toxicity of treatment was compared with that in children with lymphoblastic leukaemia receiving the same protocol.³ Only two of 15 children became febrile during induction, in contrast to 85% of those with leukaemia. The incidence of fever and gastrointestinal toxicity during intensifica-

tion was, however, similar. During the continuation of the treatment there were eight episodes of fever and neutropenia among the children with lymphoma, and there was one case each of varicella, *Pneumocystis carinii* pneumonitis, and candida pneumonia.

Discussion

These results show that a satisfactory outcome can be achieved in children with mediastinal (T cell) lymphoma using a regimen similar to that recommended for acute lymphoblastic leukaemia. We confined the report to children in whom the bone marrow was not affected, because of the problems of distinguishing acute lymphoblastic leukaemia from non-Hodgkin's lymphoma in children with marrow disease. Although this distinction may be an arbitrary one, we wanted to ensure that all the cases included would be unequivocally categorised as lymphoma.

The first reported improvements in survival in this disease were those of Wollner *et al* who used a complicated multiple drug regimen,⁵ the efficacy of which was subsequently confirmed by the American Children's Cancer Study Group.⁶ Workers at the St Jude Children's Hospital reported a 73% four year, event free survival for stage III and IV disease using a leukaemia protocol together with tenoposide and cytarabine.⁷ Our results confirm that a satisfactory response to treatment can be obtained without recourse to long term rotating drug schedules. The benefits of a comparatively simple and familiar approach are obvious, although it should be noted that this form of treatment is not suitable for the other types of childhood non-Hodgkin's lymphoma, which are largely tumours of B cell origin.

Despite the intensity of induction and consolidation, the short term toxicity of treatment was acceptable; as expected there were less infective problems during induction than in children with acute lymphoblastic leukaemia, because in no child was the bone marrow affected initially. Our results were achieved without local irradiation, which was given to only one child as emergency treatment for mediastinal obstruction. It seems that if chemotherapy is sufficiently intensive, local irradiation is not necessary to achieve either remission or long term survival. Treatment to the central nervous system is essential because of the tendency of lymphoma to recur in the central nervous system, and our patients received cranial irradiation and intrathecal methotrexate. The morbidity of cranial irradiation is well described, and it remains to be established whether intrathecal and systemic chemotherapy will provide an effective and less toxic substitute.

The results of this pilot study suggest that the UKALL X protocol is an effective treatment for mediastinal non-Hodgkin's lymphoma without bone marrow involvement. The protocol has since been adopted by the UKCCSG for national use so that confirmation of its efficacy and assessment of results in patients with stage IV disease should ultimately be available.

Event free survival in study patients and historical controls. The number of children who have been followed up for longer than 10 years is shown in parentheses.

Drs Wheeler and Chessells are supported by the Leukaemia Research Fund. We thank Miss S Taylor for typing the manuscript, and Dr S Richards for statistical advice.

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