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Isolated testicular relapse in acute lymphoblastic leukaemia of childhood

Report on behalf of the Medical Research Council's working party on leukaemia in childhood

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SUMMARY The presentation, method of treatment, and follow-up of 29 apparently isolated testicular relapses in 522 boys entering Medical Research Council trials I-III are described. The need for intensive local and systemic treatment is stressed. The prognosis is poor for those with high initial leucocyte counts, and for those with testicular relapse while on chemotherapy. Among the remainder, intensive local and systemic treatment can result in some long-term remissions.

Of the 60 cases of testicular infiltration previously reported (522 boys entered in UK ALL trials I-III between August 1970 and December 1974), 29 occurred during the first remission without other sign of leukaemic recurrence.[1] No treatment guidelines for testicular relapse had been laid down in the protocols of the trials, and as a result a variety of treatments was given. These treatments, their results, and related clinical data have been analysed retrospectively.

Results

Clinical presentation and diagnosis. The swelling of the testis was bilateral in 9 cases and unilateral in twenty. The firmness of the swelling was reported by most observers, but in only 2 patients was it painful. Twenty (69%) patients had completed their course of 2–3 years' chemotherapy, while 9 were still on treatment 10–36 months after diagnosis (Table).

The diagnosis was established by orchidectomy in 12 cases, and by biopsy in 15 (5 needle aspirates and 10 wedge biopsies), but no histological confirmation was attempted in two.

In 10 cases tissue from only one testis was examined, but of 17 in which both were examined, 11 had bilateral infiltration, leaving 6 cases with a negative biopsy from the testis of normal size.

Local treatment of the testis. Six patients were treated with unilateral orchidectomy alone, of whom 4 developed infiltration of the other testis after 6, 7 (confirmed at necropsy), 18, and 22 months. Seventeen patients received radiotherapy in dosages from 900 to 2500 rad (Table) to the whole scrotum and inguinal regions, of whom 4 had subsequent testicular relapse 2, 5, 8, and 23 months later. In these 4, initial radiation dosages had been 900, 2000, 1000, and 2500 rad respectively. In 6 cases, unilateral orchidectomy was followed by standard field scrotal irradiation in dosages from 1400 to 2400 rad. None has subsequently relapsed in the opposite testis. There was a trend towards lower irradiation dosages for those relapsing locally than for those not relapsing, but it is not possible with groups containing so few to determine the significance of this difference, although it is important to note the single testicular relapse after 2500 rad.

Subsequent systemic treatment. The local control of the infiltrate was considered important, but the possibility that such deposits could re-seed the marrow or the central nervous system was not fully appreciated at that time. Therefore, systemic therapy after testicular relapse was variable in this series. One patient received no chemotherapy until relapse 3 months later. Twelve patients received 'reinduction' with vincristine and prednisolone for 3–4 weeks; in 5 of them this was followed by standard maintenance with 6-mercaptopurine and methotrexate and pulses of vincristine and prednisolone; three had multiple drug intensified maintenance and 4 had no further treatment. Eleven patients were restarted on their previous protocol without a specific 're-induction' phase. The remaining 5 patients were

Table *Age and white cell count at presentation of acute lymphoblastic leukaemia, time of testicular relapse, its diagnosis, treatment, and follow-up, in 29 boys with isolated testicular relapse. (Patients are grouped according to status post-relapse)*

Case	Age (years) ALL diagnosed	Initial WBC ($\times 10^9/l$)	Testicular relapse					Follow-up		
			Time since diagnosis (months)	Diagnosis	Radiation dose (rad)	Subsequent chemotherapy		Subsequent relapse	Post-test remission (months)	Patient alive
						Duration (months)	Type			
1	6	2·1	37	Orch	—	24	Int+I/T	0	64+	Alive (64+)
2	6	3·2	42	Orch	2000	18	As before	0	51+	Alive (51+)
3	3	5·0	35	Biopsy	1500	24	Int	0	54+	Alive (54+)
4	6	17·5	39	Biopsy (N)	1800	24	As before	0	79+	Alive (79+)
5	11	18·0	50	Biopsy (N)	2500	24	As before	0	57+	Alive (57+)
6	7	2·3	29	Biopsy	1500	0·75	Reind only	H (+M)	8	Alive (62+)
7	7	5·0	55	Orch	—	12	As before	T+H	18	Alive (68+)
8	5	8·9	35	Orch	1500	Until relapse	As before	M (×2)	18	Alive (58+)
9	2	14·9	34	Biopsy (N)	2500	24	As before	H	33	Alive (57+)
10	1	2·4	27	Biopsy	1500	Until relapse	Reind+as before	H	5	Died (10)
11	1	2·5	27 (on Rx)	Clin	1500	Until relapse	Int	H	2	*Died (5)
12	4	4·4	36	Biopsy	2500	24	Reind+as before	T→H	23	Died (44)
13	9	4·9	25 (on Rx)	Orch	—	Until relapse	Reind+Int	H	16	Died (22)
14	4	6·0	27 (on Rx)	Orch	—	Until relapse	Reind+Int	T	6	Died (20)
15	5	7·0	51	Orch	2400	Nil	Nil	Nodal	3	Died (19)
16	2	7·0	22 (on Rx)	Orch	1400	Until relapse	As before	H	2	Died (3)
17	4	7·3	29	Orch	—	Until relapse	As before	H	8	Died (14)
18	2	13·9	35	Orch	1500	Until relapse	As before	M	15	Died (51)
19	5	17·8	27	Biopsy (N)	2500	Until relapse	As before	H	3	Died (6)
20	3	18·5	26 (on Rx)	Orch	1500	Until relapse	Reind+Int	H	3	Died (7)
21	12	26·3	16 (on Rx)	Orch	—	Until relapse	Int	H	2	Died (7)
22	2	38·5	33	Biopsy	1000	0·75	Reind only	H	6	Died (29)
23	13	39·7	21 (on Rx)	Biopsy	2000	Until relapse	Reind+as before	T	5	Died (8)
24	6	41·0	44	Biopsy	1200	0·75	Reind only	H	7	Died (36)
25	10	42·8	10 (on Rx)	Clin	1600	Until relapse	Reind only	H	1	Died (7)
26	2	67·0	30	Biopsy (N)	2500	Until relapse	As before	M	11	Died (17)
27	2	71·7	13 (on Rx)	Biopsy	900	Until relapse	Reind+as before	T+M	2	Died (9)
28	2	83·9	46	Biopsy	1000	3	Reind+as before	T+H	8	*Died (18)
29	4	251·0	32	Orch	—	Until relapse	Int+I/T	T	20	Died (37)

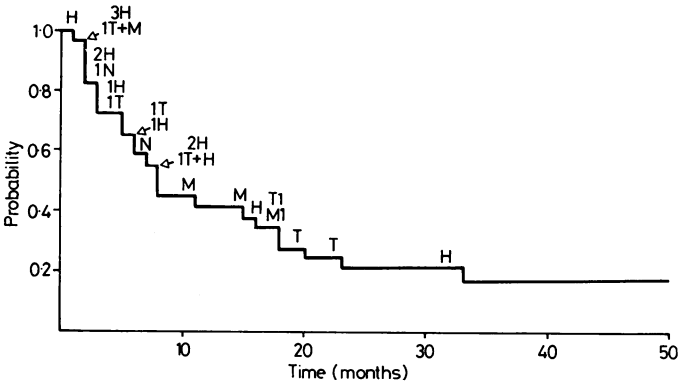
*Died in remission.
On Rx = testicular relapse while on initial chemotherapy, Orch = orchidectomy, Biopsy (N) = needle biopsy/rest or wedge, Clin = clinical diagnosis, Reind = reinduction (vincristine + prednisolone only), Int = intensified multiple drug therapy, I/T = intrathecal medication–methotrexate, H = haematological relapse, M = meningeal relapse, T = testicular relapse. N = total survival after testicular relapse.

given more intensive therapy, including multiple drug combination 'induction' (prednisolone, vincristine, asparaginase, adriamycin/daunomycin, and cytosine arabinoside). If maintenance was given it was continued until the next relapse in 16 patients, for 3 months in one, 1 year in one, 18 months in one, and 2 years in six (Table).

Next relapse. All but 5 patients have suffered a further relapse (Table), either in the bone marrow (13 cases), central nervous system (3 cases), or testes (5 cases). There were two combined relapses, and one patient developed cervical, para-aortic, and mesenteric nodal enlargement at 3 months: that patient was the only one who had no further chemotherapy. Of the 4 receiving 'reinduction' chemotherapy only, all had early haematological relapse but this also occurred when therapy was intensive and more prolonged. Only 2 of the 29 patients received further prophylaxis to the central nervous system; one with intrathecal methotrexate and one with intrathecal methotrexate plus cytosine arabinoside. The last patient has a cerebral lesion, identified on computerised tomography scan, but without an excess of cells in the cerebrospinal fluid (probably not leukaemic in origin) and the other patient has had a further testicular relapse.

Three of the 5 cases still disease-free are from the group of 11 who started the same chemotherapy as before the relapse but without specific 'reinduction', and the other 2 are from the group of 7 who were treated with multiple drug combination therapy. All are now off treatment, having received 18–24 months' extra chemotherapy after testicular relapse. The disease-free survival after testicular relapse in the 29 cases is shown in Fig. 1.

Survival. Fig. 2 shows the 4-year total survival curve. Twenty out of the 29 patients have died, with a range of survival from 3 to 51 months after the



H=haematological relapse, T=testicular relapse, M=meningeal relapse

Fig. 1 *Disease-free survival after isolated testicular relapse (n=29).*

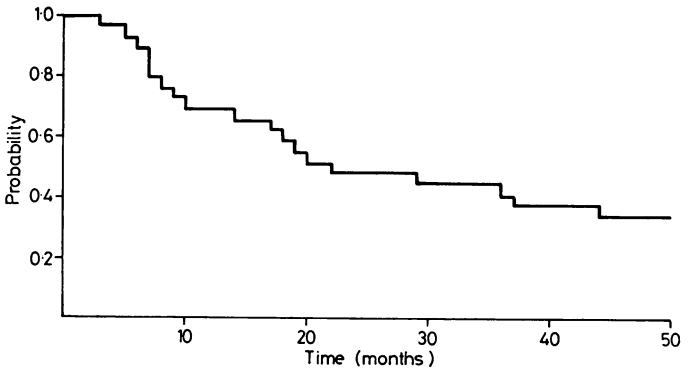


Fig. 2 *Total survival after isolated testicular relapse in 29 boys with acute lymphoblastic leukaemia.*

testicular relapse. Of these, 2 died in remission, having had at least one relapse after the testicular infiltration was diagnosed. Four patients are still living, having suffered at least one further relapse (Cases 6–9, Table) with survival periods after initial testicular relapse of 57, 62, 58, and 68 months respectively, and 5 are alive without subsequent relapse at 51–79 (median 57) months. We cannot yet be certain about the long-term survival of these 5 as second relapses have been reported more than 4 years after testicular relapse, and the last patient to stop chemotherapy did so only 25 months ago.

Discussion

It has been known for many years that the prognosis after isolated testicular relapse in acute lymphoblastic leukaemia is variable with consequences ranging from rapid relapse in the bone marrow to prolonged disease-free remissions as the two extremes.[2 3] In this series of somewhat heterogeneous patients whose relapses were managed in various ways, it is difficult to reach any precise conclusions. However, all those with initial high leucocyte counts (20×10^9/l), and all those with testicular relapse while still on chemotherapy have experienced further relapses and none has survived. Of the remainder, most of those who relapsed within 3 years from initial diagnosis have relapsed again, whereas late testicular relapsers have fared somewhat better. From this series, it would seem that local control can be guaranteed only if orchidectomy and scrotal irradiation, or irradiation in dosages of at least 2500 rad is used.[3] Current policy in the MRC trials is to perform bilateral wedge testicular biopsies on all boys at 2 or 3 years on treatment, before a decision is made about stopping maintenance. In the case of positive biopsies or the development of overt testicular swelling the recommended treatment is to irradiate the remaining testis (if orchidectomy has been performed) or both testes, to a dose of at least 2500 rad, to reinstitute full chemotherapy—'remission induction', consolidation, and maintenance for 2 years—and to give 5 further doses of intrathecal methotrexate.

Tiedemann *et al.*[4] have shown this approach to be highly effective at least in the short term, with 100% disease-free survival at 18–54 months for a series of 10 boys. Four of their series were diagnosed early by biopsy of an unenlarged testis. Earlier diagnosis and more vigorous and consistent therapy may well improve the outcome of testicular relapse. At the same time, prevention either by more intensive chemotherapy or perhaps by testicular irradiation may be a better prospect, especially for the poor risk cases. Recent trials are testing these concepts.

We thank all members of the working party who have allowed us to publish data on their patients, and Dr Chessells for helpful advice.

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Commentary

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This article describes the outcome in boys with acute lymphoblastic leukaemia (ALL) who were entered into the first three Medical Research Council UK ALL trials and in whom the first remission ended in an apparently isolated testicular relapse. Twelve years ago testicular leukaemia had been described but the extent of the problem was not fully recognised and, unfortunately, in these early protocols, no clear recommendations for treatment were given. Nevertheless, some guidelines about management and prognosis can be drawn from this retrospective analysis.

Boys who develop overt testicular infiltration while still on chemotherapy have a uniformly poor prognosis[1 2] and almost invariably develop later marrow relapse. Such patients therefore should receive local and systemic treatment followed by bone marrow transplant if a suitable donor is available.

The majority of patients who develop testicular relapse do so within the first 2 years after treatment has been electively stopped,[3] or are found to have occult testicular infiltration on routine biopsy performed before a decision about stopping treatment. The outcome for such patients may be rather better and some, given optimal treatment, may have a chance of long-term disease-free survival.

Effective local control of testicular leukaemia may be achieved by orchidectomy or radiotherapy. A dose of 2400 rad is necessary for local control of testicular disease.[4 5] One patient in Eden's study developed local recurrence after this dose but details of his systemic treatment are not clear, and we continue to prefer radiotherapy to the more traumatic alternative of orchidectomy. Presumably local control will prove easier in patients with occult (biopsy positive) infiltration. In view of the high incidence of bilateral infiltration[1] radiotherapy should be given to both testicles.

Although the bone marrow and cerebrospinal fluid may be apparently normal at the time of testicular relapse, patients who receive local treatment or minimal additional systemic chemotherapy are at risk of subsequent bone marrow or central nervous system (CNS) relapse.[1] Extensive staging investigations, including lymphography and laparotomy, in a small group of boys with apparently isolated testicular relapse, showed that some had involvement of para-aortic nodes indicating that disease was widespread.[6] It is thus apparent that intensive systemic reinduction, consolidation, further chemotherapy, and further CNS prophylaxis are essential. Despite this evidence that testicular leukaemia is but a 'marker' of residual disease elsewhere, we find at this hospital that boys with a positive biopsy or with late overt infiltration treated with bilateral local irradiation, intrathecal methotrexate, intensive reinduction, and further chemotherapy do much better than those with late bone marrow relapse: 10 of 11 boys so treated remain in second complete remission and off treatment 35 to 70 months from the time of testicular relapse.[7]