Survival and the HL-A System in Acute Lymphoblastic Leukaemia

SYLVIA D. LAWLER, P. T. KLOUDA, P. G. SMITH, MORWENNA M. TILL, R. M. HARDISTY

British Medical Journal, 1974, 1, 547-548

Summary

The relation between the HL-A antigens and survival has been studied in 58 patients with acute lymphoblastic leukaemia. Patients with the HL-A9 antigen had the best estimated median survival times, the highest ratio of survivors to non-survivors, and the lowest median age at diagnosis. The data suggest that resistance to acute lymphoblastic leukaemia may be associated with the HL-A9 antigen.

Introduction

Several groups have studied the question whether any particular HL-A phenotype or genotype is associated with an increased risk of acute lymphoblastic leukaemia. The reports have been conflicting. An analysis was made by Walford *et al.* (1971) of data on 214 patients typed for HL-A antigens. An increase in either the HL-A2 or the HL-A12 antigen or both was found in most studies but the summed results for all the patients were not statistically significant after correcting the probability value for the number of comparisons being made. Rogentine *et al.* (1972) found a significant increase in the frequency of HL-A2 in 50 Caucasion children with the disease. Most studies of the distribution of the HL-A antigens in acute lymphoblastic leukaemia have been concerned with the relation of HL-A phenotypes to susceptibility rather than prognosis. In our previous study, however (Lawler *et al.*, 1971), there was a suggestion of a good prognosis for patients with the W27 antigen (formerly FJH), which was present in three out of the five patients who had lived for four years or more at the time of testing. This paper reports the follow-up study of the relation between HL-A antigens and survival in that group of 58 patients.

Department of Cytogenetics and Immunology, Division of Medicine, Royal Marsden Hospital and Institute of Cancer Research, London S.W.3

SYLVIA D. LAWLER, M.R.C.P., F.R.C.PATH., Consultant Immunologist
P. T. KLOUDA, PROM.BIOL., Lecturer

Cancer Epidemiology and Clinical Trials Unit, Department of Health and Social Security, Oxford

P. G. SMITH, B.SC., Statistician

Department of Haematology, Institute of Child Health, Hospital for Sick Children, London W.C.1

MORWENNA M. TILL, M.B., D.C.H., Senior Research Fellow
R. M. HARDISTY, F.R.C.P., F.R.C.PATH., Professor of Haematology

Patients and Methods

The HL-A phenotypes and genotypes of the 58 patients were reported previously (Lawler *et al.*, 1971). The group consisted of all patients available at that time and was therefore heterogeneous so far as the clinical stage of the disease was concerned and included both long-term survivors and recently diagnosed cases. At the original HL-A typing the antigens W15 and W17 were both included in LND. In a later serological analysis, however, the two specificities could be distinguished, and in this report they are listed as separate antigens.

The median lengths of survival were calculated in complete weeks from the date of diagnosis to the end of November 1973, at which time 18 patients were alive and 40 were dead.

Results

The median age of the patients at diagnosis, their estimated median survival time, and the number alive and dead at the time of analysis are shown for each HL-A antigen in table I. The antigens are ranked in order of decreasing median survival. The median survival times shown do not give the true median survival of all patients with a particular antigen, as the patients in this study were typed for HL-A at varying times after the initial diagnosis and must therefore have survived from the time of diagnosis to that of the HL-A test to be included. This bias, however, should affect all the antigen groups similarly if survival is unrelated to HL-A type.

TABLE I—*HL-A Antigens and Survival*

HL-A Antigen	No. of Patients Positive	% Frequency	Median Age at Diagnosis (Years/Months)	Median Survival (Weeks)	No. Living	No. Dead
9	9	15·5	3/8	340*	6	3
W27	10	17·2	3/10	209	2	8
11	9	15·5	4/5	185	3	6
8	13	22·4	4/1	165	6	7
W15	7	12·1	4/5	165	3	4
3	14	24·1	4/4	158	1	13
5	7	12·1	5/10	156	2	5
12	22	37·9	4/1	155	7	15
2	26	44·8	4/10	154	8	18
W19	13	22·4	4/4	152	4	9
W17	2	3·4	5/6	136*	1	1
13	3	5·2	4/5	131	0	3
1	21	36·2	4/5	130	9	12
7	18	31·0	3/11	129	3	15
W14	4	6·9	5/4	129	0	4
W10	4	6·9	4/7	128	1	3
W28	7	12·1	5/2	116	1	6
10	8	13·8	6/6	100	1	7

*Median survival may be increased on further follow-up.

When four different HL-A antigens were detected the patient was recorded four times in table I; when only three different HL-A antigens were detected the patients appear three times. A homozygote was entered only once for each antigen detected—for example, a patient HL-A1,8/1,8 was recorded once for HL-A1 and once for HL-A8.

Patients with the HL-A9 antigen had the longest median survival times and the lowest median age at diagnosis. On the other hand, the shortest median survival time was found among patients with the HL-A10 antigen, and they had the highest median age at diagnosis. The median age at diagnosis for the whole sample was 4 years 6 months and the median length of survival 154 weeks.

The median survival times of patients with HL-A haplotypes that occurred more than twice are shown in table II. Any patient had a chance of being recorded twice. Nine patients were scored twice—for example, there were two of genotype HL-A2,12/3,7. The HL-A1,8/1,8 homozygote was scored only once. The HL-A9,7 haplotype showed the best median survival. The HL-A1,8 haplotype was apparently associated with the lowest median survival, but four of the 10 patients were still living at the end of November 1973.

In our previous study interest had focused on patients with the W27 antigen as potential long-term survivors. In table I the patients with the W27 antigen are shown to rank second so far as median age and survival are concerned. The age at diagnosis, length of survival, and mortality for the 10 patients with the W27 antigen are shown in table III. Of the two patients still alive at the end of November 1973 one had already survived for more than eight years.

TABLE II—*HL-A Haplotypes and Survival*

Haplotype	No. of Patients	Median Age at Diagnosis (Years/Months)	Median Survival (Weeks)	No. Living	No. Dead
9,7	3	3/5	255*	2	1
W19,12	4	3/11	242*	2	2
3,7	8	4/3	197	1	7
2,W15	3	4/2	165	0	3
2,12	8	4/10	162	2	6
10,12	3	3/8	130	1	2
1,7	3	6/5	127	0	3
1,8	10	5/1	104	4	6

*Median survival may be increased on further follow-up.

TABLE III—*W27 Antigen and Survival*

Case No.	Age at Diagnosis (Years/Months)	Survival in Weeks	Living or Dead
1	2/10	261	D
14	6/10	76	D
20	1/4	104	D
23	1/11	185	D
41	11/6	77	D
44	3/5	80	D
48	3/2	232	D
51	7/8	425	L
52	4/3	188	L
56	5/2	299	D

Discussion

In the previous study we investigated the possibility of an association between susceptibility to acute lymphoblastic leukaemia and the HL-A system. The subjects of that first series consisted of all patients with the disease attending hospital during the period May 1970 to January 1971. Thus the clinical stage of the disease varied. The population included five patients who had lived for four years from diagnosis, of whom three had the W27 antigen. The present analysis of the HL-A system in relation to survival was made 34 months after that study was concluded.

The length of survival in acute lymphoblastic leukaemia is related to clinical and haematological findings at diagnosis, clinical management, and response to therapy. Any effect of the HL-A system must interact with these factors.

The patients with the W27 antigen ranked second according to median length of survival (table I), but by the end of November 1973 only two of these 10 children were still alive (see table III). Median survival, though a reasonable summary measure, may be misleading. The survival data on the patients with the W27 antigen show four short-term survivors and six long-term ones, with a gap in the intermediate range. A slight difference in the data could have caused a substantial change in median survival. Ranking median survival times in groups with the same HL-A antigen also produces a ranking, more or less, according to median age at diagnosis (table I). We cannot explain this and, moreover, in the series as a whole there was no relation between age at diagnosis and duration of survival.

Patients with the HL-A9 antigen had the best median survival time, the highest ratio of survivors to non-survivors, and the lowest median age at diagnosis. Since six of the nine patients were still alive at the end of November 1973 the median survival point was not reached. When survival after the date of HL-A testing is considered those with the HL-A9 antigen are shown to have survived significantly better ($P<0.05$) than those without this antigen. Similarly, patients with the HL-A3 antigen survived significantly worse ($P<0.05$) than those without this antigen. No other differences are significant. But when survival is considered from the date of first treatment then none of the differences are statistically significant. These significance levels take no account of the number of tests performed, and if this were done then none of the differences would remain significant.

The data do perhaps provide some limited support to the idea that resistance to acute lymphoblastic leukaemia may be associated with the presence of the HL-A9 antigen. A decreased frequency of this antigen in patients with this disease was observed by Batchelor *et al.* (1971), Rogentine *et al.* (1972), Sanderson *et al.* (1974), and Klouda *et al.* (1974). Possibly children with the HL-A9 antigen are less susceptible to acute lymphoblastic leukaemia than are those lacking the antigen; furthermore, if they do develop the disease they have a better prognosis. Since this observation is based on relatively few data further studies of this kind would be of great interest.

This work was supported in part by a grant from the Leukaemia Research Fund.

Requests for reprints should be addressed to Dr. Sylvia D. Lawler.

References

Batchelor, J. R., Stuart, J., and Edwards, J. H. (1971). *Lancet*, **1**, 699.
Klouda, P. T., Lawler, S. D., Till, M. M., and Hardisty, R. (1974). *Tissue Antigens*. In press.
Lawler, S. D., Klouda, P. T., Hardisty, R. M., and Till, M. M. (1971). *British Journal of Haematology*, **21**, 595.
Rogentine, G. N., Yankee, R. A., Gart, J. J., Nam, J., and Trapani, R. J. (1972). *Journal of Clinical Investigation*, **51**, 2420.
Sanderson, A. R., Mahour, G. H., Jaffe, N., and Das, L. (1974). *Transplantation*. In press.
Walford, R. L., Smith, G. S., and Waters, H. (1971). *Transplantation Reviews*, **7**, 78.