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THE INFLUENCE OF CHEMOTHERAPY ON THE MANAGEMENT OF NON-HODGKIN'S LYMPHOMATA AT THE PRINCESS MARGARET HOSPITAL

A COMPARISON OF THE RESULTS FROM 1962–64 WITH 1967–69

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Summary.—A retrospective study of 460 non-Hodgkin's lymphoma patients seen in 1962–64 (185) and 1967–69 (275) revealed a marked improvement in the survival of patients treated during the later interval. The increased survival was not due to differences in the age or sex distribution of patients, the proportions with systemic symptoms or extranodal presentations. The improvement was due partially to a disproportionate increase in the number of patients with well- and intermediately differentiated nodular lymphocytic lymphomata in 1967–69. When these patients were removed, the proportions of patients with " good " and " poor " pathology were comparable for the two intervals, and a markedly improved survival was still evident for the 1967–69 group. An improvement in the proportion of patients achieving a complete remission occurred only in patients who received some form of chemotherapy. Relapses occurred in 44·6% of patients with Stage I and II disease treated with radiotherapy alone. The results of this study indicate that we must re-evaluate carefully the indications for radiotherapy in the treatment of the non-Hodgkin's lymphomata. The addition of chemotherapy appears to be a promising method for increasing the proportion of patients who will achieve a long complete remission.

WE HAVE made a retrospective study of patients with non-Hodgkin's lymphoma who received primary treatment at The Princess Margaret Hospital in 1962–64 and have compared them with patients treated in 1967–69. The survival of patients treated during the second interval was considerably better than that of patients treated in 1962–64 (Fig. 1). The purpose of this study was to identify the factors which contributed to this improved survival.

PATIENTS AND METHODS

All previously untreated patients over the age of 17 years with biopsy material available for review by one of us (T.C.B.) who received primary treatment at The Princess Margaret Hospital in the interval of 1 January 1962 to 31 December 1964, or 1 January 1967 to 31 December 1969, were included in this study. The reasons for excluding patients and the proportions of suitable patients who had biopsies reviewed are shown in Table I.

The hospital records of all patients considered for this study were reviewed, and details regarding symptoms, physical findings, operative reports, radiological and laboratory investigation, radiotherapy and chemotherapy, and the response to treatment were extracted on special forms. Patients with a persistent absolute lymphocyte count of more than 5440/mm^3 were considered to have chronic lymphocytic leukaemia (Ibbott and Whitelaw, 1966) and were excluded. Standard criteria were used to exclude patients with acute lymphoblastic or myelomonoblastic leukaemia (Bodey and Freireich, 1972). Patients with lymphomatous invasion of the marrow or with leukosarcoma cells in the peripheral blood were not excluded.

The staging system recommended by Peters, Hasselback and Brown (1968) for nodal and extranodal non-Hodgkin's lymphomata was used. The pathology classification recommended by Moran *et al.* (1975) was followed. The results of the pathology review have been presented in detail elsewhere (Brown *et al.*, 1975). Follow-up information to 31 December 1972 was available for all but one of the patients treated in 1962–64 and for all but 12 of the 1967–69 group.

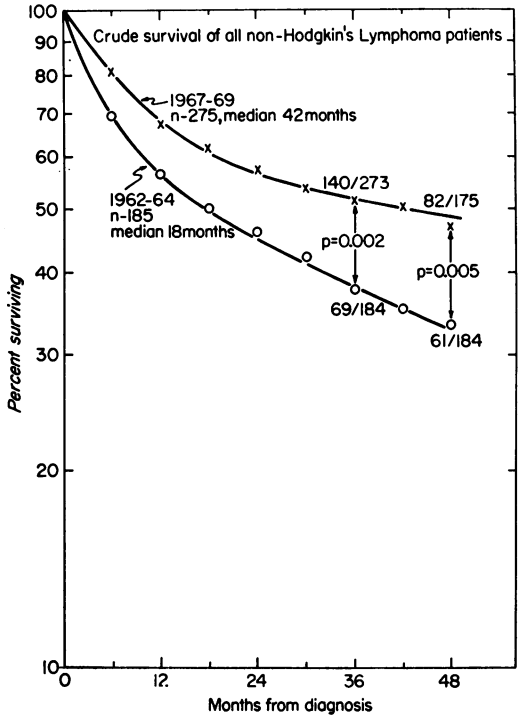

FIG. 1.—Crude survival from diagnosis of all non-Hodgkin's lymphoma patients seen in 1962–64 and 1967–69. The ratio of the number of patients alive/number at risk and the significance of the differences are shown at 36 and 48 months.

TABLE I.—*Admission of Non-Hodgkin's Lymphomata to Study*

	1962–64	1967–69
Patients over 17 years, presumably " suitable "	319	415
Excluded:		
(a) After chart review		
prior treatment	6	13
no biopsy	1	1
diagnosis at autopsy	1	1
data on chart inadequate	1	1
(b) After pathology review		
leukaemia	24	20
other neoplastic disease	1	3
not neoplastic	5	1
" Suitable "	280	375
Pathology review done	185	275
Proportion of " suitable " patients in study	66·1%	73·3%

Comparisons of the proportions of patients comprising different groups, or surviving at 3 or 4 years from diagnosis were made using the *chi* square test with the Yates correction for small numbers. Survival was measured from the date of biopsy diagnosis because the interval between diagnosis and the onset of treatment was variable and tended to be longer in the patients with slowly progressive disease.

RESULTS

Age and sex

The age and sex of the patients in the 2 intervals is shown in Table II. The median age was similar for the patients in the 2 groups. The proportion of females was greater in 1967–69 (48·4%) than in 1962–64 (42·7%). The females in this series lived considerably longer than the males and we wondered whether the slightly increased proportion of females in the 1967–69 group contributed to their better survival. For males, the surviving fraction at 3 years from diagnosis increased from 35/105 (33·3%) in 1962–64 to 65/140 (46·4%) in 1967–69, while for females the surviving fractions increased from 35/79 (44·3%) to 75/133 (56·4%) for the same intervals. Since the improvement in survival is similar for both males and females, it is unlikely that the increased proportion of females in 1967–69 was a significant factor in the overall improvement in survival.

TABLE II.—*Age and Sex of Non-Hodgkin's Lymphoma Patients Included in Study*

	1962–64		1967–69		
Age	Male	Female	Male	Female	Total
< 20	—	1	1	2	4
20–29	7	2	11	7	27
30–39	15	9	12	14	50
40–49	17	13	25	19	74
50–59	19	17	38	25	99
60–69	27	17	31	34	109
70–79	16	20	19	27	82
80–89	4	—	5	5	14
> 90	1	—	—	—	1
Total	106	79	142	133	460
Median age (years)	56	59	57	58	58

Investigation

Patients were investigated more extensively in 1967–69 than in 1962–64 (Table III). All patients probably had chest x-rays before starting therapy; for a few patients, however, this examination was made at another hospital and a report of the result could not be found in The Princess Margaret Hospital record. The proportion of patients having marrow examinations and laparotomies did not change appreciably between 1962–64 and 1967–69, but there was a marked increase in the frequency of all other investigations listed in Table III. Laparotomies on patients in this study were carried out mainly to investigate the cause of an abdominal mass, or an acute intestinal obstruction, in patients with abdominal lymphoma who had no recognized peripheral nodes available for biopsy.

TABLE III.—*Initial Investigation of Non-Hodgkin's Lymphoma Patients*

	1962–64		1967–69	
Investigation	No.	(%)	No.	(%)
1. Chest x-ray	170	91·9	276	97·1
2. Bone marrow	101	54·6	138	50·2
3. Laparotomy	52	28·1	63	22·9
4. Lymphogram	5	2·7	126	45·8
5. Intravenous pyelogram	18	9·7	105	38·2
6. Inferior venacavagram	—	—	28	10·2
7. Mediastinal tomograms	2	1·1	49	17·9
8. Bromsulphalein retention	8	4·3	74	26·9
9. Serum alkaline phosphatase	45	24·3	222	80·7
10. Liver scan	—	—	83	39·2
11. Spleen scan	—	—	49	17·8

Staging

Because of the marked difference in the methods used to investigate patients during the 2 intervals it is not possible to compare the clinical stages. As a result of the more extensive investigation during 1967–69, an increased proportion of patients with advanced disease was recognized (Table IV).

The presence of systemic symptoms of fever, night sweats and weight loss carries a poor prognosis. Since the enquiry regarding these symptoms was similar during the 2 periods, it is of interest that there is no significant difference in the proportions of patients with systemic symptoms in 1962–64 and 1967–69. Also, there was no improvement in the survival of patients with systemic symptoms; the major improvement occurred in patients without these symptoms (Table IV).

There was no difference in the proportions of patients who presented with extranodal primaries during the 2 intervals, nor in the proportions of these patients alive at 3 years. The major improvement in survival occurred in patients with nodal disease.

Pathology

The distribution of pathology by year of admission is shown in Table V. The major differences in the composition of the 2 groups are the increased proportions in 1967–69 of patients with nodular

TABLE IV.—*Presentation and Stage of Disease Before Therapy*

Presentation	1962–64 $n = 185$ %	Difference	1967–69 $n = 275$ %
Stages: I and II	50·8		45·1
III and IV	49·2		54·9
" B " Symptoms: Present	31·4	N.S.	26·9
alive at 3 years	17·2	N.S.	16·2
Absent, alive at 3 years	47·6	$P = 0·001$	64·5
Site: Extranodal	31·4	N.S.	32·0
alive at 3 years	36·8	N.S.	40·9
Nodal, alive at 3 years	37·8	$P < 0·001$	56·2

N.S.—not significant, $P > 0·005$.

TABLE V.—*Pathology by Years of Admission*

Pathology	1962–64 No.	1962–64 (%)	1967–69 No.	1967–69 (%)	Total
Lymphocytic, well differentiated and intermediately differentiated					
Diffuse	22	11·9	22	8·0	44
Nodular	8	4·3	32	11·6	40
Lymphocytic, poorly differentiated and mixed lympho-" histiocytic "					
Diffuse	88	47·6	85	30·9	173
Nodular	20	10·8	43	15·6	63
Undifferentiated, non-Burkitt, diffuse	8	4·3	11	4·0	19
Undifferentiated, Burkitt	—	—	1	0·3	1
" Histiocytic "					
Diffuse	35	18·9	71	25·8	106
Nodular	2	1·1	8	2·9	10
Unclassified	2	1·1	2	0·7	4
Total	185	100·0	275	100·0	460

patterns (30·1% *vs* 16·2% in 1962–64), and those with " histiocytic ", diffuse disease (25·8% *vs* 18·9% in 1962–64), and the reduced proportion of patients with lymphocytic, poorly differentiated and mixed lympho " histiocytic " diffuse disease (30·9% *vs* 47·6% in 1962–64).

It is well known that the well differentiated lymphocytic lymphomata, and those with a nodular pattern have a better prognosis than the other types of non-Hodgkin's lymphomata. For purposes of comparing the composition of patients in the 2 periods, we have divided them (Table VI) into those with " good " pathology (*i.e.*, pathology groups with more than 45% alive at 3 years) and " poor " pathology (less than 45% alive at 3 years). Although the proportion of patients alive at 3 years for 1967–69 increased in most of the pathology groups, the major improvement occurred in patients with the nodular lymphomata other than the lymphocytic, well- and intermediately differentiated types.

The proportion of patients with " good " pathology was greater in 1967–69 (105/275 = 38·2%) than in 1962–64 (52/185 = 28·1%); this difference is significant ($\chi_2 = 4{\cdot}55$, $P = 0{\cdot}022$), and is due mainly to the disproportionate number of patients with lymphocytic, well- and intermediately differentiated, nodular lymphomata seen in 1967–69. When these patients are subtracted from the patients with " good " pathology, the proportions with " good " pathology do not differ significantly: 44/177 (24·9%) in 1962–64 and 73/243 (30·0%) in 1967–69 ($\chi_2 = 1{\cdot}12$, $P = 0{\cdot}309$). Despite the removal of this group of patients with nodular lymphoma and a good prognosis, the survival of patients treated in 1967–69 is consistently better than those treated in 1962–64 (Fig. 2). The proportion of the 1967–69 patients alive is significantly greater than the 1962–64 group at 3 years ($P = 0{\cdot}025$) and 4 years ($P = 0{\cdot}008$).

Thus, although the increased proportion of patients with nodular, well- and intermediately differentiated lymphocytic lymphomata in 1967–69 contributed to the better survival of the total series of patients treated during this interval, this contribution is not sufficient to totally explain the improvement.

Treatment

The initial form of treatment is shown in Table VII. The proportion of patients treated initially with radiation alone did not change during the 2 periods. The major change was to treat more patients with combination chemotherapy during 1967–69. A considerable number of drug combinations were used but the commonest was intermittent cyclophosphamide

TABLE VI.—*Survival at 3 Years by Pathology*

Pathology	1962–64 % alive at 3 years	Difference	1967–69 % alive at 3 years
" Good "	63·5	N.S. ($P = 0·07$)	78·1
LW and ID Diffuse	68·2	N.S.	72·9
Nodular	100	N.S.	90·6
Other nodular	45·5	$P = 0·039$	72·6
" Poor "	27·8	N.S.	34·1
L, PD and mixed, diffuse	33·0	N.S.	41·2
" H " diffuse	22·9	N.S.	29·6
Undifferentiated and unclassified	0	N.S.	14·3
Total	37·5	$P = 0·002$	51·3

N.S.—not significant, $P > 0·05$.

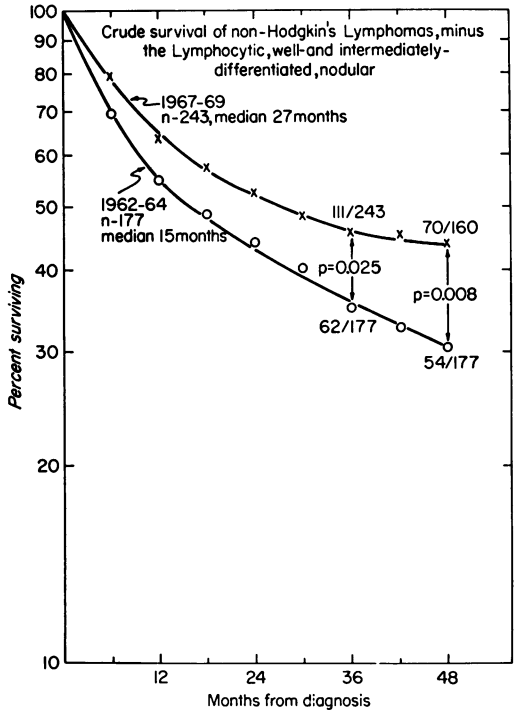

FIG. 2.—Crude survival from diagnosis of non-Hodgkin's lymphomata minus the well- and intermediately differentiated lymphocytic, nodular types for 1962–64 and 1967–69. The ratio of the number of patients alive/number at risk and the significance of the differences are shown at 36 and 48 months.

and vincristine, together with prednisone and procarbazine.

Some form of chemotherapy was eventually used in 76 of 180 patients (42·2%) started in 1962–64, and in 123 of 267 patients (46·1%) started in 1967–69. The proportion of patients who received

TABLE VII.—*Initial Treatment*

Initial treatment	1962–64 No.	1962–64 (%)	1967–69 No.	1967–69 (%)
R	127	68·7	190	69·1
R + P	2		5	
R + S	20	17·8	8	9·1
R + S + P	10		3	
R + C	1		9	
P	3		2	
S	10		11	
S + P	5	10·8	17	18·9
C	2		22	
No treatment	5	2·7	8	2·9
Total	185	100·0	275	100·0

R—radiation; P—prednisone; S—single agent other than prednisone; C—combination chemotherapy.

combination chemotherapy at some time in their treatment increased from 11/180 (6·1%) in 1962–64 to 72/267 (27·0%) in 1967–69.

We have chosen to evaluate the effectiveness of treatment by comparing the proportions of patients who achieved complete remissions (no evidence of disease by clinical, radiological, haematological and biochemical examination). For this evaluation (and subsequent analysis shown in Tables VIII–XI), we excluded all patients with lymphocytic, well- and intermediately differentiated, nodular lymphomata, in order to make the proportions of patients with " good " pathology comparable for the 2 periods. The proportions of these patients who achieved a complete remission are shown in Table VIII. The percentage achieving complete remissions increased significantly, from 41·9% in 1962–64 to 53·2% in 1967–69 ($P = 0·02$).

TABLE VIII.—*Comparison of Complete Remissions in Non-Hodgkin's Lymphomata, Minus the Well- and Intermediately Differentiated Lymphocytic, Nodular, by Year of Admission and Treatment*

	1962–64			1967–69	
	No.	%	Significance of difference	No.	%
Total treated	172	100		235	100
Complete remission	72	41·9	$P = 0·02$	125	53·2
(a) Radiation alone	61	35·5	N.S.	95	40·4
(b) Radiation + chemotherapy	8	4·7	N.S.	16	6·8
(c) Chemotherapy alone	3	1·7	$P = 0·05$	14	6·0
(d) b + c.	11	6·4	$P = 0·04$	30	12·8

N.S.—not significant, P greater than 0·05.

TABLE IX.—*Complete Remissions Lasting for More Than 2 Years*

	1962–64			1967–69	
Complete remissions and treatment	No.	%	Significance of difference	No.	%
CR > 2 years/Total CR	41/72	56·9	$P = 0·034$	90/125	72·0
(a) CR > 2 years/CR by radiation alone	35/61	57·4	N.S.	66/95	69·5
(b) CR > 2 years/CR by radiation and chemotherapy	5/8	62·5	N.S.	14/16	87·5
(c) CR > 2 years/CR by chemotherapy alone	1/3	33·3	N.S.	10/14	71·4
(d) CR > 2 years/CR by (b) + (c).	6/11	54·6	N.S.	24·30	80·0

N.S.—not significant, P greater than 0·05.

TABLE X.—*Initial Stage of Disease for Patients Achieving Complete Remission with Radiotherapy Alone*

Stage	Complete remission No. of patients	Relapse No.	Relapse %
I	70	23	32·9
II	60	35	58·3
III	21	18	85·7
IV	5	3	60·0
Total	156	79	50·6

The combined total of all non-Hodgkin's lymphoma patients, minus the well- and intermediately differentiated, lymphocytic, nodular types achieving a complete remission following radiotherapy alone are listed by the initial stage of disease. The relapses which have occurred to date are recorded, together with the percentage of relapses for each stage. Of the relapses, 55 occurred during the first 2 years after the completion of treatment and 24 after 2 years.

TABLE XI.—*Sites of Relapse Following Complete Remission Induced by Radiotherapy for Stages I and II*

Site of relapse	Patient No.	% of CR Total—130
Within irradiation field	5	3·8
Outside irradiation field	53	40·8
(a) Nodal	34	
(b) Extranodal	16	
(c) Multiple (nodal and extranodal)	3	
No relapse	72	55·4

The sites of relapse for the Stage I and II patients who achieved a complete remission following radiotherapy alone (as shown in Table X) are listed. The percentages of all patients with Stage I and II disease who achieved a complete remission following radiotherapy and have since relapsed, or remained in remission, are also shown.

We next looked at the method of treatment that was used to achieve a complete remission. The proportion of all treated patients who achieved a remission by a particular form of treatment was used for the comparison of results between the 2 periods, rather than the proportion of patients who were treated with each form of treatment, because we were interested in determining the contribution of each type of treatment to the overall results. (In 1962–64 84 patients were treated with radiotherapy alone, 73 received radio-

therapy plus chemotherapy and 15 were treated with chemotherapy alone. In 1967–69, 110 received only radiotherapy, 92 radiotherapy plus chemotherapy and 33 chemotherapy alone.)

It is of interest that the increase in the proportion of patients achieving a complete remission following radiotherapy alone did not increase significantly. It was only in the patients treated with chemotherapy alone that a significant improvement in the complete remission rate occurred. The frequency of complete remissions in the combined group of those treated with radiotherapy plus chemotherapy, and with chemotherapy alone, also increased significantly. It should be noted that chemotherapy was used only for patients with advanced Stage III and IV disease, while radiotherapy was used mainly for Stage I and II disease.

The complete remissions induced during 1967–69 were better than those of 1962–64 because the proportion lasting for more than 2 years increased from 41/72 (56·9%) for 1962–64 to 90/125 (72·0%) for 1967–69 (Table IX). Although the proportion of remissions lasting for more than 2 years increased for each form of treatment, the improvement was not significant for any of the treatment categories.

When the patients achieving a complete remission with radiotherapy in 1962–64 and 1967–69 are combined, we find that 79 of 156 have relapsed. The initial stage of the lymphoma and the frequency of relapse are noted in Table X. The majority of patients achieving a complete remission after radiotherapy alone presented initially with Stage I and II disease. The relapse rate was smallest in the patients who presented in Stage I and increased progressively for Stage II and III.

The sites of relapses in the Stage I and II patients treated with radiotherapy alone are shown in Table XI. Radiotherapy controlled the disease in 55·4% of patients. The occurrence of relapse outside the irradiated area indicates that treatment to a single region was inadequate to control the disease in 44·6% of these patients.

DISCUSSION

The purpose of this retrospective study was to identify the factors contributing to the improved survival of the non-Hodgkin's lymphoma patients treated in 1967–69. A disproportionate increase in the numbers of patients with well- and intermediately differentiated, nodular lymphocytic lymphomata in 1967–69 was partially responsible. With the removal of these patients, the proportions with "good" and "poor" pathology are comparable in 1962–64 and 1967–69; in these patients, the improved proportion achieving a complete remission in 1967–69 was due primarily to the treatment of more patients with some form of chemotherapy.

Patients seen in 1967–69 were investigated more extensively, but the proportion of patients treated initially with radiotherapy did not alter. The major change in the approach to treating patients with radiotherapy in 1967–69 was a policy to use wide fields in the treatment of abdominal lymphomata, especially those presenting with a primary lesion in the gastrointestinal tract and regional (mesenteric) node involvement (Jenkin *et al.*, 1969; Bush and Ash, 1969). Despite this change, a significant improvement in the proportion of patients who achieved a complete remission following radiotherapy alone was not observed.

We also found that 44·6% of patients with Stage I and II lymphomata who achieved a complete remission following radiotherapy alone relapsed, with a recurrence outside the treatment fields in 40·8%. This observation suggests that local therapy is inadequate for the control of a significant proportion of patients with apparently localized disease.

The results of this retrospective study make it apparent that the indications for

radiotherapy in the treatment of non-Hodgkin's lymphomata must be re-evaluated carefully. We need to find more effective methods for inducing complete remissions of long duration. The use of combination chemotherapy (Bagley *et al.*, 1972), wide field irradiation (Jenkin *et al.*, 1969; Bush and Ash, 1969) and a combination of chemotherapy and radiotherapy appear to be promising approaches to achieve this aim.

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