PROGNOSTIC FACTORS IN LOW GRADE LYMPHOMA (Study of 278 Cases)

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Introduction and Aim of The Work

Non-Hodgkin's lymphomas are a diverse group of tumours which show morphologically a heterogenous wide spectrum of disease complexes and often unpredictable response to treatment. Clinically they vary from fulminate conditions to chronic indolent processes (Jelliffe, 1986).

According to the Working Formulation, the NHLs are grouped into three broad prognostic categories, low, intermediate and high grade diseases. Low grade NHLs are composed of three histologic subtypes by the Working Formulation: small lymphocytic (SLL), follicular small cleaved cell (FSCL) and follicular mixed small cleaved and large cell (FML).

Whereas radiotherapy is potientially curative in localized disease (stage I and II), the most appropriate management of wide-spread lymphoma remains controversial. Current therapeutic modalities range from a cautious "Watch and Wait" approach, through chemotherapy of moderate intensity, to aggressive multidrug regimens combined with total nodal irradiation (Young et al., 1988 and Portlock, 1990).

The aim of this work is review of different treatment modalities of newly diagnosed low grade NHL patients with analysis of the prognostic factors for response and survival.

Materials and Methods

278 patients with previously un-

treated low grade NHL formed the basis of retrospective analysis of the present study. These patients were treated at Royal Marsden Hospital, Surrey, England, over the period from 1970 to 1989 inclusive.

All patients were staged according to Ann Arbor Staging Classification, the only modification was the subdivision of stage II into 2 subgroups, localized and extensive, patients were classified as stage II localized when two contiguous nodal regions or an extranodal site and regional nodes on the same side of the diaphragm were involved, when more than 2 nodal regions were involved or when non-contiguous involvement was present, patients were classified as stage II extensive.

At initial presentation, 92 patients were treated with chemotherapy, 33 patients received single agent chlorambucil and 59 patients received combination chemotherapy which included 28 patients receiving Lop, it was given in 4 weeks cycles for average 6 cycles as follows:

- Chlorambucil 6mg/m^2/day P. O. days 1-14.
- Oncovin 1.4 mg/m^2 I.V. day I.
- Prednisolone 40mg/m^2 P.O., days 1-14.

Cop was given to 6 patients, it was given in the same dosage with substitution of cyclophosphamide (600mg/m^2) I.V. days 1 and 8 or 400mg/m^2 P.O. days 1-5, instead of chlorambucil.

Chlvpp was given to 6 patients in 4 weeks cycles for average 6 cycles as follows:

- Chlorambucil 6mg/m^2 P.O. days 1-14,
- Vinblastine 6mg/m^2 I.V. days 1 and 8,
- Procarbazine 100mg/m^2 P.O. days 1-14,
- Prednisolone 40mg/day P.O. days 1-14.

Five patients received Copp which was given in the same dosage as Chlvpp but using cyclophosphamide instead of chlorambucil, 600mg/m^2 I.V. days 1 and 8, only one case received Mopp in which nitrogen mustared (6mg/m^2 IV days 1 and 8) was used instead of chlorambucil. Four cases received CHOP which was given in 3 weeks cycles as follows:

- Cyclophosphamide 750mg/m^2 IV day 1,

- Adriamycin 50mg/m^2 I.V. day 1,
- Oncovin 1.4mg/m^2 I.V. day 1,
- Prednisone 20mg/day P.O. days 1-5.

Five cases were treated with BACOP, only one case received CHOP-M in which methotrexate was added while the remaining three patients received other regimens.

Of the radiotherapy treated group (84 patients), 36 patients were treated with invovled field, 36 patients with extended field and 10 patients with total body irradiation (TBI). The median prescribed tumour dose was 40 Gy for invovled field and 38 Gy for the extended field using conventional fractionation of 2 Gy per fraction, 5 daily fractions per week. For TBI, the midplane dose was 1.5 Gy usually delivered as sequential upper half body irradiaiton followed by lower half body irradiaiton after 6 weeks.

Radiotherapy was delivered using linear accelerator (5 to 8 Mev) in 64 patients and cobalt^{60} in 20 patients.

Twinty eight patients were treated with combined chemotherapy and radiotherapy. They included 11 patients treated with invovled field radiotherapy, 9 patients with extended field and 8 patients were treated with total body irradiation.

Complete remission (CR) was defined as the disappearance of all signs and symptoms of the disease as determined by clinical, radiological and laboratory evaluation. Partial remission (PR) was defiend as a reduction of 50% or more of measurable disease for at least one month. No response (NR) i.e. failure; any other responses including mixed response. stable disease, progressive disease, or death due to toxicity was considered as failure. Not assessable (NA). was applied to cases managed with watch policy or cases without measurable disease or abnormal investigation to assess.

Survival was computed from the date of initial diagnostic biopsy to date of death or date of last follow up. Progression free survival (PFS) was computed from the date of starting initial treatment or date of treatment plan of watch policy group to the date of subsequent progression of the disease. Survival and progression free survival curves were constructed by the life table method of Kaplan and Meier, (1958).

The statistical difference were evaluated by the Log-Rank test (Peto et al., 1977). Multivariate analysis for survival and PFS was carried out using Cox's proportional hazyards model (Cox, 1972).

Results

Patient's characteristics of 278 low grade NHL patients are shown in table (1). The median age was 57 years, the age ranged was 19 to 85 years, 57 patients (20%) were stage I, 42 patients. (15%) were stage II, 66 patients (24%) were stage III and 133 patients (41%) were stage IV. 134 cases were nodal only (48%) while 144 cases were extranodal (52%).

Bone marrow was invovled in 88 cases (32%). The distribution of different histological types was SLL in 43 cases, (165). FSCL in 176 cases (63%) and FML in 59 cases (21%). Of the 92 patients treated with chemotherapy, the median survival of single agent and combination chemotherapy groups was 4.6 years and 5.4 years respectively which was statistically insignificant (x^2=0.09 df = I, P>0.1). The corresponding figures of median. PFS was 2.1 years and 1.5 years respectively which was also statistically insignificant (X^2=0.10, df = I, P>0.1).

Of 88 patients who were assessable for response, 31 patients (35%) had complete response and 47 patients (53%) had partial response and the remaining 10 cases (12%) had no response, with overall response rate of 88%. The median survival was longer in patients treated with adriablastin based regimens, 7.5 years, compared with 5.5 years of patients treated with LOP or Cop, 5 years of patients treated with chlorambucil, however this difference was statistically insignificant (X^2=0.07, df = 3, P>0.1). Again, median PFS was longer in MOPP treated patients, 2.4 years, than 0.9 year of patients treated with ADR based regimens, 1.4 years of patients treated with LOP and 2.1 years of patients treated with chlorambucil which was also statistically insignificant (x^2=4.13, df = 3, P>0. 1).

The median survival and median PFS of 84 patients treated with radiotherapy were 13 years and 4.7 years respectively, survival at 5 and 10 years was 81% and 62% respectively, PFS at 5 and 10 years was 49% and 34% respectively, This difference was statistically significant, (X2=20.6, df=I, P<0.005).

Median PFS of both groups was 7.2 years and 1.4 years respectively, again the difference was statistically significant (X2=8.77, df=I, P<0.005).

Twenty eight patients received combined chemotherapy and radiotherapy, they included 4 patients (14%) with stage I,7 patients (25%) with stage II,7 patients (25%) with stage III and 10patients (36%) with stage IV. Three patients were SLL (11%), 17 patients (61%) were FSCL and 8 patients (28%) were FML. The median survival and PFS of entire group were 5.3 years and 3.2 years respectively, 5 and 10 years survival were 57% and 38% respectively while PFS at 5 and 10 years was 34% and 26% respectively. The complete response was seen in 20 patients (74%) and PR in 7 patients (26%) and one case showed no response.

The actuarial survival of the entire group was 64% at 5 years and 46% at 10 years. The median survival was 8.75 years.

Of the different modalities received, survival of the radiotherapy group (median 13 years) was longer than combined modality group (median 5.2 years). Single agent chemotherapy (median 4.6 years) and combined chemotherapy group (median 5.4 years), the difference was statistically significant (X^2=14.07, df=3, P<0.005). PFS of the radiotherapy group (median 4.5 years) and combined modality group (median 3 years) was longer than PFS of single agent chemotherapy group (median 2.1 years) and combined chemotherapy group (median 1.5 years). The difference was statistically significant, (X^2=13.75, df=3, P<0.005), meanwhile there was no statistical difference between radiotherapy and combined treatment groups or between single and combination chemotherapy groups (Table 2).

By univariate analysis of prognostic variables affecting survival, old age (>60 years), advanced clinical stage (III, IV), more than 2 sites of the disease, extrandoal disease, Hb level, <11.5 gm% and treatment with chemotherapy were highly significant adverse prognostic variable (P<0.005): less significant adverse prognostic variables included β symptoms, (P<0.025), bone marrow involvement (P<0.025) and ESR >40 ml/hr (P<0.01), sex, histology, liver involvement and bulk of disease were non-significant, these results are summar-

ized in table (3). By multivariate analysis, the number of sites of the disease was the most important variable followed by age and Hb level. Treatment modality didn't have any further significance as a prognostic variable.

The entire group of patients is divided into 4 groups according to the number of poor prognostic variables identified by multivariate analysis (i.e. >2 sites, age >60 years and Hb <11.5 gm%). The median survival of 13 patients with non of poor prognostic variables has not been reached, while it was 13.4 years for 103 patients with one variable, 5.5 years for 134 patients with 2 variable and 2.4 years for 28 patients with 3 poor prognostic variable. The difference was statistically significant (P<0.005).

The overall PFS of the entire group was 35% and 25% at 5 and 10 years respectively. The median PFS was 2 years and 2ms. By univariate analysis of prognostic variables affecting PFS, more than 2 sites of disease, extranodal disease, bone marrow involvement, advanced clinical stage and treatment with chemotherapy were highly significant adverse prognostic variable (P<0.005) less adverse variables included liver involvement. (P<0.025), Hb level <11.5 gm% (P<0.025) and old age >60 years (P<0.05). Sex, histology, β-symptoms and bulk of disease were non-significant (Table 4).

By multivariate analysis, more than 2 sites of disease was the most important variable followed by extranodal disease, treatment modality did not have any further significance as a prognostic variable.

Table (1) : Characteristics of 278 low grade NHL patients .

Characteristic	No. of patients	Percentage (%)
Age :		
Median = 57 years		
range = 19 to 85 years		
Sex :		
Male	128	46%
Female	150	54%
β- Symptoms :		
A	233	84%
B	45	16%
Histology :		
SLL	43	16%
FSCL	176	63%
FML	59	21%
Site of disease :		
Nodal only	134	48%
Extranodal	144	52%
Bone marrow invovlement :		
Negative	172	62%
Positive	88	32%
Unassessed	18	6%
Stage :		
I	57	20%
II	42	15%
III	66	24%
IV	113	41%
Treatment :		
Watch policy	74	27%
Chemotherapy	92	33%
Radiotherapy	84	30%
Combined modality	28	10%

Table (2) : Survival of 278 low grade NHL patients according to treatment modality .

Treatment modality	No. of patients	Percentage	Survival			Significance	Death	Survival			Significance
			5 Ys	10 Ys	15 Ys			5 Ys	10 Ys	15 Ys	
Single agent	33	25	19	13	6	P>0.1	18	50	25	25	P>0.1
Comb. chemotherapy	59	45	20	18	18		39	52	31	23	
Single agent	33	25	19	13	6		18	50	25	25	
ADM based	10	8	30	20	20	P>0.1	6	57	43	21	P>0.1
MOPP	12	7	33	33	33		9	58	25	25	
LOP/COP	34	28	13	13	13		22	50	35	26	
Radiotherapy	84	51	50	35	30		38	82	62	42	
Single agent	33	25	19	13	6	P<0.005	18	50	25	25	P<0.005
Comb. chemotherapy	59	45	20	18	18		39	52	31	23	
Comb. radiochemo.	28	18	35	26	26		18	57	38	25	

N.B. : 74 patient s were managed with watch policy .

Table (3) : Univariate analysis of prognostic variables affecting survival of 278 low grade NHL patients

	Number		Survival %			Significance
	Patients	Deaths	5 years	10 years	15 years	
All patients	278	148	64	46	31	
Age : < 60 years	161	69	75	48	43	
> 60 years	117	79	50	29	11	p>0.01
Sex : Male	128	66	60	44	26	p>0.01
Female	150	82	67	47	34	
Histology : SLL	43	26	56	31	26	
FSCL	176	94	64	47	31	p>0.1
FML	59	28	72	51	33	
Number of sites :						
1-2 sites	87	29	85	68	49	p<0.005
> 2 sites	189	118	55	35	22	
Site of disease :						
Nodal only	134	64	72	57	40	p<0.005
Extranodal	144	84	57	33	20	
Bone mrrow involvement:						
Negative	190	95	70	52	35	p<0.025
Positive	88	52	52	31	21	
Liver involvement :						
Negative	251	129	66	47	32	p>0.1
Positive	27	19	51	37	18	
β- Symptoms :						
A	233	120	68	49	31	p<0.025
B	45	28	43	28	28	
Hb level :						
= < 11.5 gm%	34	25	40	26	13	p<0.005
> 11.5 gm%	219	112	67	46	33	
ESR : < 40 mm	144	73	64	48	36	p<0.01
= > 40 mm	26	21	61	19	0	
Diameter of largest mass:						
< 5 cm	124	67	62	41	30	
5 - 10 cm	33	19	53	36	36	p>0.1
> 10 cm	5	2	60	60	60	
Stage at presentation :						
Stage I/II	99	36	81	68	48	p<0.005
Stage III/IV	179	112	55	33	20	
Intended treatment :						
Watch policy	74	35	64	52	25	
Chemother apy	92	57	51	28	24	p<0.005
Radiotherapy	84	38	81	62	41	
Combined modality	28	18	57	38	25	

Table (4) : Univariate analysis of prognostic variables affecting the PFS of 278 low grade NHL patients

	Number		Survival %			Significance
	Patients	Deaths	5 years	10 years	15 years	
All patients	278	189	35	25	22	
Age : < 60 years	161	108	38	29	26	
> 60 years	117	81	30	20	16	p<0.05
Sex : Male	128	87	35	24	22	p>0.1
Female	150	102	35	27	22	
Histology : SLL	43	28	29	24	24	
FSCL	176	123	35	24	20	p>0.1
FML	59	38	38	33	28	
Number of sites :						
1-2 sites	87	46	59	45	34	p<0.005
> 2 sites	189	143	22	15	15	
Site of disease :						
Nodal only	134	80	48	37	32	p<0.005
Extranodal	144	109	21	12	11	
Bone mrrow involvement:						
Negative	190	121	43	30	26	p<0.025
Positive	88	68	17	14	12	
Liver involvement :						
Negative	251	165	37	28	24	p<0.025
Positive	27	24	21	9	4	
β- Symptoms :						
A	233	159	37	26	22	p>0.1
B	45	30	21	21	21	
Hb level :						
= < 11.5 gm%	34	25	20	16	8	p<0.005
> 11.5 gm%	219	149	36	26	22	
ESR : < 40 mm	144	94	38	29	29	p= 1
> 40 mm	26	22	23	9	0	
Diameter of largest mass:						
< 5 cm	124	84	32	26	24	
5 - 10 cm	33	33	28	15	15	p>0.1
> 10 cm	5	3	40	40	40	
Stage at presentation :						
Stage I/II	99	56	54	41	32	p<0.005
Stage III/IV	179	133	23	16	15	
Intended treatment :						
Watch policy	74	50	36	25	20	
Chemother apy	92	70	19	16	14	p<0.005
Radiotherapy	84	51	49	34	29	
Combined modality	28	18	34	26	26	

DISCUSSION

Low grade NHL is one of the most controversial subject in Oncology especially its management, because of lack of curative treatment and lack of survival benefit of currently used treatment approaches. The present study is one of the large series of low grade NHL patients treated and followed up in one institution over a period of 20 years. Clinical characteristics of the present study are consistent with large series of low grade NHL (Soubeyran et al., 1991).

The optimal treatment for low grade NHL has still to be defined, the full range from no-treatment to aggressive combined modality treatment has been suggested, (Portlock et al., 1987 and Young et al., 1988).

The median survival and PFS of patients treated with single alkylating agents (chlorombucil) of the present series was not statistically different from that of combination chemotherapy group as reported by Hoppe et al. (1981), again there was no statistical difference of survival and PFS between different combination chemotherapy regiemens as reported by Lepage et al. (1990).

Radiotherapy is reported to have curative potential for patients with localized stage I, II, L.G.L. and to have substantial palliative efficacy in patients with more advanced stage (Carabell et al., 1978 and Paryan et al., 1984).

Five and 10 years survival of stage I and II patients treated with radiotherapy of the present series are 93% and 79% respectively and the corresponding figures of PFS are 59% and 43% respectively which are consistent with reports of Gospodarowicz et al., (1984).

However, in our series, age was only significant prognostic factor affecting survival as non of the factors examined has an impact on PFS. The need of adjuvant chemotherapy in a stage I, II low grade lymphoma is stil uncertain and should be evaluated especially in clinically staged patients. 5 years survival and PFS of advanced stage III and IV LGL are 77% and 27% respectively which dropped dramaticaliy to 27% and 15% respectively, these results indicate that radiation has a palliative role in the management of advanced low grade NHL.

In the present study PFS of radio-

therapy group (median 4.5 years) and combined modality group (median 3 years) was significantly different from that of chemotherapy group with no difference between radiotherapy and combined modality groups or between single and combined modality groups.

However mulivariate analysis treatment modality did not have any further significance as prognostic variable. This is explained by the fact that 69% of radiotherapy group had localized disease compared with 39% of combined modality group and 9% of chemotherapy group.

The practice of watch policy in the management of low grade NHL is based on the observation that most of these patients are without life threatening disease at the time of diagnosis and that current treatment do not result in cure. In present study 74/278 (27%) of patients were judged to be asymptomatic and eligible for watch policy approach which is similar to 22/92 (24%) of patients reported by Leisveld et al. (1991).

The median survival of the group was 10.2 years which is similar to Horning and Rosonberg series 1984 (11 years).

Many prognostic factors were reported to affect response to treatment and survival of low grade NHL 'patients. Patients with localized stage I and II, and young age were reported to have favourable outcome, Leonared et al., (1991) and Soubeyran et al. (1991).

Anaemia, male sex and poor performance status were also reported to adversely affect survival (Leonard et al., 1991). β-symptoms, hepatosplenomegaly, anaemia, and abnormal liver function tests were also reported by Gallaglier et al. (1986) to be poor prognostic factors affecting survival.

In present study number of sites of disease (<=3 sites) was the most important poor prognostic variable identified by multivariate analysis followed by age (>=60 years) and Hb level (<=II.5 gm%). Stage and number of sites of disease are highly correlated. According to these prognostic variables it is possible to get a good idea of prognosis by simply assessing the patients age, number of sites of disease and Hb level. 4 subgroups of patients could be identified with different survival outcome. Our results are similar to that reported by Leonard et al. (1991). However, in the present ser-

ies, performance status was not assessed and gender was not significant prognostic variable.

In the present series more than 2 sites of disease and extranodal disease were important variables identified by multvariate analysis to affect PFS three subgroups of patients could be identified with different PFS outcome.

Summary and Conclusions

During the period between January 1970 and December 1989 inclusive 278 newly diagnosed low grade NHL. Patients were treated and followed up at the Royal Marsden Hospital Surrey, England, the median survival and PFS was 8.75 years and 2.5 respectively (median follow-up = 8 years). The median survival of patients managed with radiotherapy group (13 years) was longer than that of Watch policy group (10.2 years) combined modality group (5 .2 years) and chemotherapy group (5 years), the difference was statistically significant ($P<0.005$). Median PFS of radiotherapy, watch policy, combined modality and chemotherapy group were 4.5 years, 2 years, 3 years and 1.8 years respectively which is statistically significant difference ($P<0.005$). Of the chemotherapy group there was no significant difference in survival or PFS between patients treated with single alkylating agent and chemotherapy or between different combination chemotherapy regimens.

By univariate analysis, age (>60 years) stage (III and IV), more than 2 sites of disease, extranodal disease, anemia, β-symptoms, bone marrow involvement and ESR >40 mm/h and chemotherapy treatment were adverse prognostic factors affecting survival. By multivariate analysis, more than 2 sites of disease, age (>60 years) and anaemia remained as significant adverse prognostic factors. For PFS, old age, advanced stage, more than 2 sites of disease, extranodal disease, bone marrow involvement, liver involvement, anaemia and chemotherapy treatment were univariate adverse prognostic factor. By multivariate analysis more than 2 sites of disease and extranodal disease remained significant. Treatment modality does not have any further significance as a prognostic factor.

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الملخص العربى

يمثل هذا البحث دراسة لعدد ٢٧٨ حالة أورام غدد ليمفاوية غير هودجكن منخفضة الدرجة تم علاجها ومتابعتها فى مستشفى رويال مارسدن بانجلترا على مدى عشرون عاماً فى ا لفترة من ١٩٧٠ حتى ١٩٨٩ وذلك لتقييم طرق العلاج المستخدمة فى هذه الأورام.

وشملت طرق العلاج : الكيماوى (٩٢ حالة) والإشعاعى (٨٤ حالة) والكيماوى - الإشعاعى المشترك (٢٨ حالة) إضافة إلى ٧٤ حالة أخرى تم ملاحظتها بدون علاج حتى حدوث تغيرات مرضية تستدعى ذلك.

وقد تم دراسة تحليلية لمعرفة نسبة الاستجابة (الكلية والجزئية) كذلك متوسط بقاء المريض الكلية وتلك بدون تدهور مرضى لمجموع الحالات الكلى ثم لكل مجموعة على حدة ومقارنتها بالمجموعات الأخرى وشمل هذا التحليل العوامل المرضية المختلفة التى تتحكم فى فترة بقاء المريض الكلية وبدون تقدم مرضى حيث تم تحليل هذه العوامل فردياً ومجتمعة.

ونتيجة لهذه الدراسة فقد تم إستخلاص النتائج التالية :

- بلغ متوسط بقاء المريض الكلية ٨ر٧٥ عاماً وتلك بدون تدهور مرضى، ٢ر٢ عام.
- أهم العوامل المرضية التى تتحكم فى فترة بقاء المريض هى عدد المجموعات الليمفاوية المصابة بالورم وعمر المريض ونسبة الهيموجلوبين فى الدم.
- لم تتأثر فترة البقاء (الكلية وتلك بدون تدهور مرضى) جوهرياً باستخدام طرق العلاج المختلفة.