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Hodgkin's Disease (HD): A Historical Perspective

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Abstract—*Five hundred and seven patients with Hodgkin's lymphoma (HL), forming the basis of our 18 years experience, are retrospectively analyzed. Four therapeutic periods are recognizable:*

1. *The* 1966–1970 *period was characterized by the absence of treatment and management policy. The* 55 *patients entered in this period experienced* 70 *and* 56% *survival at* 5 *and* 10 yr, *respectively, from diagnosis.*
2. *The* 1971 1974 *period was characterized by the increasing knowledge of staging relevance and therapeutic approaches. The* 153 *patients who were treated in this period experienced* 72 *and* 60% *survival at* 5 *and* 10 yr, *respectively.*
3. *The* 1975–1980 *period was characterized by a large combination of MOPP and radiotherapy. The* 216 *patients who entered this period observed* 80 *and* 72.5% *survival at* 5 *and* 10 yr, *respectively.*
4. *The last therapeutic period* (1980 *to present time*) *is characterized by the increasing relevance of prognostic factors and alternating use of MOPP and ABVD as non-cross resistant regimen. The* 83 *patients who entered this period showed* 90% *survival at* 5 yr.

Both survival and disease-free survival were positively influenced by the change of therapeutic strategies during the four periods ($P < 0.005$). *Although better results have been recorded moving from one to the next therapeutic period, the present policy has been also based on the recognition of a high number of late complications due to the therapy. Preliminary results about the present therapeutic experience seem to indicate both a good remission rate and low incidence of complications.*

INTRODUCTION

INCREASING experience in the therapeutic strategies of Hodgkin's Disease (HD) has produced, during the last 20 years, concurrent improvements [1–10]. More than 70% of patients can now be cured as compared to the lower proportion who benefited in the past decades. Besides these encouraging developments, the recognition of early [11-17] and late [18-24] complications due to staging procedures or to therapy has been stressed.

Criticism of the Ann Arbor's staging system has been raised with the increasing interest in prognostic factors [8, 25–33]. These factors have been considered independently of the stage, with a more suitable definition of the prognostic risk. This led to value again the opportunity of indiscriminating laparotomy [8, 34] in all patients and of selecting different therapeutic approaches. Secondly, MOPP chemotherapy, which has been considered the appropriate treatment in HD, is responsible for some of the above mentioned complications [11, 16, 21]. Moreover, the possible usefulness of an alternative scheme in patients relapsed after MOPP induced an effort to find either a non-cross resistant or a less damaging regimen [35–37].

During our 18 years of experience involving 500 patients with HD we went through the above mentioned phases. In particular four therapeutic periods were experienced; each of them designed upon available data and our previous experience.

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The results herewith described, the side effects and trends of each therapeutic period are reported to verify the appropriateness of the past choices and to elucidate the present perspectives.

PATIENTS AND METHODS

The study includes all 507 cases of previously untreated adult patients with pathologically proved HD who were treated from January 1966 to December 1982 at the Institute of Hematology "L. e A. Seràgnoli" and Radiotherapy of the University of Bologna (Italy).

The histologic subtype was defined according to Lukes *et al.* criteria [38] and the pathologic or clinical stages were defined according to Ann Arbor's staging conference [39].

The patient population was retrospectively identified according to different treatment periods experienced in our Institutions in the last 18 years. According to the time of diagnosis, patient groups were defined in the following periods: January 1966–December 1970, January 1971–December 1974, January 1975–June 1980, July 1980–December 1982.

In addition to the comparative value of different staging procedures, therapeutic approach, clinical and pathologic aspects, each group has been analyzed according to remission rate, survival and disease-free survival. A concurrent analysis looking at the main prognostic factors such as age, stage, symptoms, bulky disease and the type of therapy was also performed. Finally, the therapy related complications are reported according to the type of therapeutic program employed.

Survival and relapse-free survival were calculated from diagnosis, and respectively, from complete remission (CR) to death and to relapse, or to June 1985; the method used was the same as was previously described by Kaplan and Meier [40].

Survival for each study period was considered at 5 and 10 year intervals, except for the last period in which only a 5 year experience was available. Differences were calculated considering the above intervals and employing the test for trend, previously described by Peto *et al.* [41].

Tables 1 and 2 report in detail the staging approaches and the therapeutic programs used during the above-mentioned periods.

In general, moving from one to another period we introduced a different management of HD, which progressively included more accuracy in detection of stage by the greater use of laparotomy with splenectomy. In the last period we restricted the use of laparotomy at diagnosis to selected patients without bad prognostic factors (large mediastinal involvement, fever or more than three involved sites).

Table 1. Principal procedures employed for staging purpose during the four therapeutic periods

Staging procedures	1966–1970	1970–1974	1975–1980	1980–1982
Chest X-rays + serial tomography	Routinely	Routinely	Routinely	Routinely
Lymphography	When subdiaphragmatic involvement was suspected	Routinely	Routinely	Routinely
Bone biopsy	Rarely with surgical technique	Routinely with surgical technique or Janshidi needle	Routinely with Janshidi needle	Routinely and twice performed in patient at risk for bone marrow involvement
Liver biopsy	Rarely when involvement was clinically suspected	Routinely during laparotomy	Routinely	Only in laparotomized patients
Laparatomy + splenectomy	When spleen involvement was suspected	Routinely	Routinely	Only in clinical stage III without bulky mediastinal disease
199 Tc bone scan	Rarely	Frequently	Routinely	Only when bone involvement was suspected
Pielography, angiography	When a great subdiaphragmatic mass was suspected	Rarely	Never	Never
CT scan	Not available	Not available	Rarely employed as alternative to lymphography	In some patients as comparative analysis vs.lymphography

With respect to therapy, in the first phase the radiotherapy consisted of local (LNI) or enlarged field radiation (ENI) and chemotherapy with single agents (Vinblastin, Cyclophosphamide, Steroids) [42]. Later our therapeutic approach was standardized according to the suggestions of Kaplan [43] concerning the radiotherapy, and the experience with combination chemotherapy [1, 2, 9, 36, 44–46]. In a successive step we employed the combination of chemotherapy and radiotherapy, to reduce the incidence of relapses among patients treated with radiotherapy alone [2, 44, 47]. Finally, we entered the last phase where more relevance has been given to prognostic factors and therapy related complications such as second tumor, sterility and post-splenectomy sepsis [11–23]. In this phase an effort has been made to investigate non-cross resistant regimens to MOPP such as ABVD [35]. For this purpose combination radiation and chemotherapy was limited to patients in stages I–II with bad prognostic factors, namely large mediastinal involvement, fever or more than three involved sites. Radiotherapy was employed alone in patients with good prognosis. Chemotherapy was programmed as alternating MOPP and ABVD. For patients in stage III with bad prognostic factors we started a therapeutic approach similar to that of stage IV, which consisted of eight courses of alternating MOPP and ABVD plus radiotherapy on bulky disease. The patients in stage III with good prognostic factors received radiotherapy alone.

In the approach to relapses we also progressively modified our policy. In the first period, in absence of an adequate therapeutic program, we had not got a clear idea; after MOPP chemotherapy was introduced, we treated all relapsed patients with this regimen. After 1975 ABVD represented an alternative treatment for patients relapsed after MOPP and finally in the last phase we are trying a new approach for patients relapsing after MOPP and ABVD, which consists of aggressive therapy

Table 2. Therapeutic protocols employed during periods under study

	1966–1970*	1971–1974†	1975–1980‡	1980–1982§
I–II A	LNI–ENI (4500R)	ENI or STNI (4500R)	ENI or STNI + 3 MOPP (4500 IF and 3600 other sites)	Without bulky mediastinal disease and less than three involved sites—ENI-STNI (4500 IF and 3600R UF)
				With bulky mediastinal disease or more than three involved sites—3 MOPP–ENI (3600R)–3 ABVD
I–II B	LNI–ENI (4500R) + vinblastine	ENI or STNI (4500 + 3 MOPP)	As above	As above
III A	LNI–ENI–TNI + vinblastine	TNI (4500R)	TNI (3600R) + 5 MOPP	Without bulky mediastinal disease—TNI (4500R IF and 3600R UF)
				With bulky mediastinal disease: eight cycles of alternating MOPP-ABVD + LNI (3600R) on mediastinal disease
III_s A–B IIIB	Vinblastine or CTX + LNI or TNI	3 MOPP-TNI-3 MOPP	5 MOPP + TNI (3600R)	eight cycles of alternating MOPP-ABVD + LNI on bulky disease
IV A–B	Vinblastine + CTX + prednisolone + LNI	6 MOPP + vinblastine for 1 year	6 MOPP	As above

*relapsed pts after 1970 received 6 cycles of MOPP + TRL.
†relapsed or resistant pts received 6 adjunctive MOPP before 1975 and thereafter 6 ABVD + TRL.
‡relapsed or resistent pts received 6 cycles of ABVD.
§relapsed or resistent pts without bone marrow involvement received intensive therapy and autologous bone marrow transplantation as hematologic rescue.
LNI = local nodal irradiation; ENI = enlarged nodal irradiation; STNI = subtotal nodal irradiation; TNI = total nodal irradiation; IF = involved fields; UF = uninvolved fields.

Table 3. Clinical and pathologic characteristics of patients in the four study periods

	(6601–7012) 55 pts	(7101–7412) 153 pts	(7501–8006) 216 pts	(8007–8212) 83 pts
Mean age	min 17 / 37.0 / max 67	min 13 / 37.6 / max 74	min 11 / 38.0 / max 76	min 15 / 33.3 / max 71
Sex	M 34 / M/F 1.6 / F 21	M 86 / M/F 1.3 / F 67	M 135 / M/F 1.6 / F 81	M 50 / M/F 1.5 / F 33
Median follow-up (months)	min 160 / 192.4	min 120 / 143.9	min 50 / 89.1	min 36 / 45.9
Histologic diagnosis				
Lymphocytic prevalence (LP)	7 (12.7%)	12 (7.8%)	13 (6.0%)	4 (4.8%)
Nodular sclerosis (NS)	31 (56.4%)	87 (56.9%)	153 (70.4%)	58 (69.9%)
Mixed cellularity (MC)	12 (21.8%)	42 (27.5%)	44 (20.4%)	20 (24.1%)
Lymphocytic depletion (LD)	5 (9.1%)	12 (7.8%)	7 (3.2%)	1 (1.2%)
Symptoms				
A	28 (50.9%)	83 (54.2%)	110 (50.9%)	56 (67.5%)
B	27 (49.1%)	70 (45.8%)	106 (49.1%)	27 (32.5%)
Stage				
I	7 } 16.3%	18 } 13.1%	30 } 15.3%	11 } 13.2%
II E	2 }	2 }	3 }	0 }
II	22 } 41.8%	47 } 34.6%	53 } 29.5%	26 } 33.7%
II E	1 }	6 }	6 }	2 }
III	10	20	22	24
III S	6 30.9%	39 38.6%	52 34.3%	12 43.3%
III E	1	0	0	0
IV	6 10.9%	21 13.6%	45 20.8%	8 9.6%
Laparotomy and splenectomy at diagnosis	15 (27.3%)	118 (77.1%)	171 (79.2%)	46 (55.4%)

followed by autologous bone marrow transplantation.

RESULTS

Table 3 shows the clinical and pathologic aspects of the 507 patients under study subdivided according to the four therapeutic periods. Minimal differences were recorded in the sex distribution. Important differences have been recorded between periods with regard to the mean age, the histologic subtype, the distribution of stage and symptoms. In particular we registered in the last period a smaller proportion of patients with B symptoms, stage IV and with Lymphocytic Depletion subtype. Furthermore, the mean age of the patients was lower in the most recent group than in the other periods.

Table 4 shows the remission rate, disease-free

Table 4. Prognostic analysis of patients with HD according to the four periods

Period		1966–70	1971–74	1975–80	1980-82	*P*-value
No. of pts		55	153	216	83	
Remission rate (%)		74.5	77.1	82.9	90.4	< 0.005
Disease-free survival (%)	5 yr	70	82.5	92	92.5	< 0.025
	10 yr	56	70	90	/	< 0.005
Survival	5 yr	70	72	80	90	< 0.005
	10 yr	56	60	72	/	< 0.005

Table 5. Prognostic analysis according to the major prognostic factors

		10 yr survival (%)	*P*-value
Age	< 40	76	< 0.025
	> 40	54	
Stage	I–II	85	< 0.005
	III–IV	52	
Symptoms	A	78	< 0.025
	B	54	
Bulky	no	84	< 0.005
	yes	51	

survival and survival experienced in the four periods. A significant improvement in each of these parameters was recorded over time. The 74.5% remission rate recorded in the first period progressively reached 90.4% in the last ($P < 0.005$). The disease-free survival ranged from 70 to 92% at the 5 year interval in the first and last period, respectively ($P < 0.025$); similarly, a significant improvement was recorded at the 10 year interval moving from the first to the third period ($P < 0.005$). The survival progressed in a similar way either at 5 years or at 10 years. Figures 1 and 2 show the disease-free survival of the four groups of patients.

Table 5 shows an analysis of the prognostic factors performed on the entire group of patients. A significantly better survival was recorded for younger patients ($P < 0.025$), with less diffuse disease ($P < 0.005$), without symptoms ($P < 0.025$) and without bulky disease ($P < 0.005$). A similar analysis performed in each period shows a progressively smaller impact on prognosis of symptoms, bulky disease and stage moving from the first and second periods to the third and fourth. Table 6 shows the prognostic analysis according to radiotherapy alone, chemotherapy alone or a

Table 6. Prognostic analysis according to the type of therapy employed

		10 years survival	*P*-value
Stage I	R×T	80	N.S.
	R×T + ChT	90	
Stage II	R×T	75	N.S.
	R×t + Cht	85	
Stage III	R×t	44	< 0.005
	ChT	44	
	R×T + Cht	65	

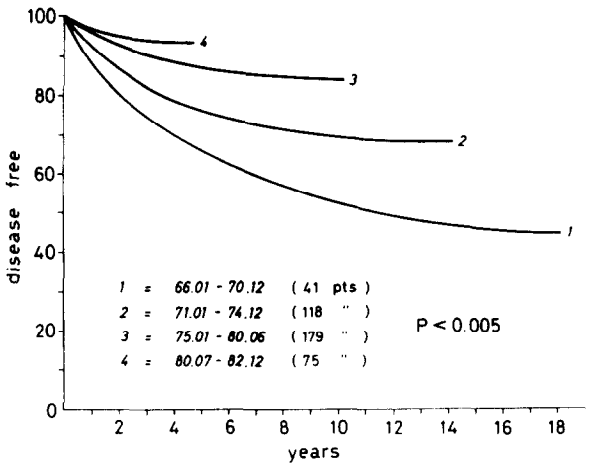

Fig. 1. Survival according to the four therapeutic periods under study.

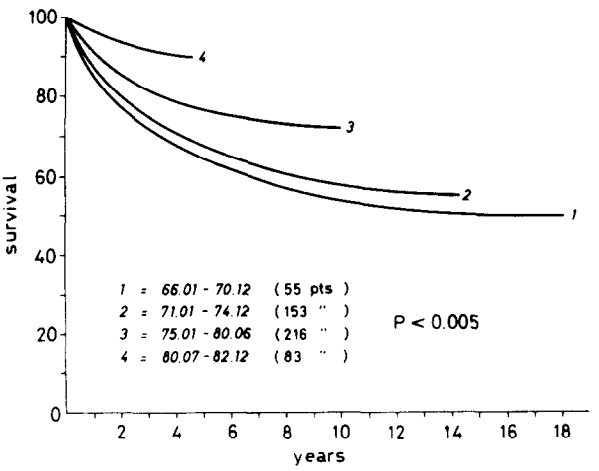

Fig. 2. Disease-free survival according to the four therapeutic periods under study.

combination of both; patients in stage IV were excluded because only few of them received combination treatment. In stage I–II the combination treatment appeared to improve, but not significantly lengthen survival. In stage III, patients who received a combination program have had a better survival ($P < 0.005$).

Table 7 reports the therapy related complications in each period. As is shown the main cause of death, other than lymphoma, was a second tumor, principally acute non-lymphoid leukemia. This complication was mainly recognized in the third period, when 12 patients developed the disease, and was exclusively associated to the combination of extended radiotherapy and more than three courses of MOPP chemotherapy. Other complications were severe lung and mediastinal fibrosis, recognized more frequently in the second period when all the patients received 4500 rads on the mediastinum. Iatrogenic aplasia after radiotherapy and MOPP was mainly recorded in the second period when our experience with MOPP was quite limited. Finally, some patients presented a post-splenectomy sepsis in complete remission and soon after the completion of the treatment.

Table 7. Distribution of non-lymphoma related deaths according to therapeutic periods under study

	No. of deaths (%)	6601–7012 3 (5.4%)	7101–7412 19 (12.5%)	7501–8006 24 (11%)	8007–8212 1(1.2%)
Causes:	Respiratory failure (lung fibrosis)		8	3	
	Post-splenectomy sepsis	2	2	1	1
	A.N.L.		1	12	
	Second tumor				
	Solid tumor		1	4	
	Iatrogenic aplasia	1	7	2	
	Others			2	

DISCUSSION

This study represents a clear demonstration of how the type of therapy can positively influence the prognosis. However, this conclusion stems from a wide analysis of all the various aspects involving the management of the patients, i.e. stage detection, prognostic factors, methods of treatment and treatment morbility. In fact in changing our therapeutic approach from time to time we always analyzed the above mentioned aspects by looking at our previous experience [4, 5, 17, 20, 32, 34, 44, 45] and at the published data [1–3, 6–19, 21–31, 34–39, 42, 43, 46–49].

With regard to the determination of stage we went through three distinct phases. The first was characterized by the lack of sufficient accuracy because laparotomy and bone biopsy were not routinely performed; obviously this gave misleading results in the stage of many patients and consequently in correct management. The second phase was characterized by the uniform employment of the main staging procedures in all patients. This yielded the data, which was possible to compare with clinical and pathologic findings and to analyze the value of laparotomy in all patients. After a careful analysis of various aspects of HD we went into the third phase in which only patients without bad prognostic factors underwent the pathologic detection of stage (laparotomy with splenectomy). As is shown these different approaches in stage detection produced some differences in the clinical presentation of the patients of the four groups, i.e. the underestimation of stage IV in the last group because of the smaller number of patients subjected to laparotomy; the other differences, such as the percentage of patients with symptoms or different age and histologic distribution are explained by a shortening of the time between the onset of signs and diagnosis. The differences, although important for a correct prognostic analysis do not invalidate our type of study which was based upon our previous experience and on other reports concerning the same field [22].

With regard to the prognostic factors, an increasing importance has been reported by many investigators who have provided information about some important factors such as age [31, 33], anatomic substages [25], bulky mediastinal disease [26, 29, 32], symptoms [28], large spleen involvement [28, 31, 33], and the number of involved sites [27, 33]. In the same way we analyzed our patients confirming what was suggested by others and finding the relevance of other factors affecting the prognosis, such as the lymphographic aspect [33]. Besides confirming the relevance of the more common factors affecting the prognosis, our analysis also shows less importance of these factors across the therapeutic periods. In fact, the presence of B symptoms during the first and second period was associated with a poor prognosis, but this was not the case in the last two periods. Similarly, a decrease of prognostic significance was recognized for the presence of bulky disease and stage. Our explanation is that the change is connected to the differentiation of therapeutic approach and particularly to more aggressive chemotherapeutic regimens for those patients bearing the above-mentioned factors. The latter aspect is further confirmed by the recognition of a similar prognosis for patients in stage I–II treated only with radiotherapy and those treated with a combination of radio–chemotherapy; obviously the last group includes patients with bad prognostic factors. Except for a few patients in stage III who underwent radiotherapy or chemotherapy alone, the majority of them received both radio and chemotherapy. The difference in therapeutic management according to prognostic factors applies only to patients treated in the last period, when a more aggressive chemotherapy of eight alternating courses of MOPP and ABVD was used. No definite conclusions on the results can be drawn, although at the 5 year interval both survival and disease-free survival appear better than recorded in the previous periods.

The last important point is the recognition of treatment and management morbility. In reco-

rding postsplenectomy sepsis we stressed the opportunity to avoid indiscriminate laparotomy. Thigh bone necrosis, severe mediastinal fibrosis and iatrogenic pericarditis induced us to reduce the radiation dose in uninvolved fields. Finally the great incidence of acute non-lymphoid leukemia in patients heavily treated with radio and chemotherapy was the most important deterrent in differentiating the therapy both according to stage and prognostic factors, possibly avoiding the overlapping effects of a combination treatment in the patients with good prognostic factors. Furthermore, in patients with stage III and bad progostic factors the use of radiotherapy has been limited only to the sites where the disease was bulky.

In conclusion our study would demonstrate how the management of HD has been changed during the years in order to progressively improve the results. In particular a correct strategy in the therapy of HD now requires a more complex definition of the prognostic risk not only based upon the stage definition according to the Ann Arbor conference [39] but on the stage plus the other prognostic factors. Subsequently the therapy should be differentiated according to the prognostic risk. Providing a similar approach certainly could reduce the number of patients at risk of second tumours.

Finally, we cannot conclude definitely if the larger use of non-cross resistant regimens such as MOPP and ABVD may produce a lower incidence of refractory patients. Although the preliminary results indicate it, we believe a further improvement in HD is to find an alternative scheme for patients refractory to a conventional one. The use of intensive and aggressive therapy followed by autologous bone marrow transplantation is now under study.

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