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Features and Prognosis of Chemotherapy-Treated Hodgkin's Disease with Initial Bone Marrow Involvement

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Summary. *The features and prognosis of Hodgkin's disease with bone marrow involvement were studied in a series of 53 patients. This form of the disease is characterized by the high incidence of clinical and biological signs reflecting disease activity, common cytopenia (which is rare in other forms), an increased incidence of the lymphocyte depletion histologic type, and extensive lymphoid involvement, often with splenomegaly. In bone marrow biopsy specimens, Sternberg-Reed cells are found in 80% of cases and fibrosis is common, though it always disappears if remission is achieved.*

Chemotherapy, essentially with the MOPP combination, produced an 82% remission rate with 44% complete remission (CR). Hematologic toxicity was relatively severe in patients with marrow fibrosis. Recurrence occurred in 14 of the 39 remissions and was either localized and successfully treated by complementary radiotherapy, or diffuse and beyond any form of therapy. In nine cases, the first sign of recurrence was observed in the lymph node group initially most affected. Among the 18 patients treated by reinduction chemotherapy, four recurrences were observed. However, there was only one recurrence among the 12 patients who achieved CR and none among those who had received complementary radiotherapy. The long-term prognosis is similar to that of other visceral forms, and if CR is achieved the chance of maintaining the remission is 83% after the first year, with a follow-up exceeding 6 years.

Introduction

Until the introduction of combined chemotherapy in 1964, visceral forms of Hodgkin's disease had an extremely poor prognosis. The MOPP regimen considerably changed the prognosis in stage IV disease, since 80% of these patients achieve remission. However, patients with initial bone marrow involvement did not appear to benefit fully by this progress, perhaps because of the particular clinical, biological, anatomical, and histological features of this form of the disease. This study shows that this is no longer true.

Materials and Methods

From 1964 to 1976 over 1200 cases of Hodgkin's disease were diagnosed and evaluated in the department of Prof. Jean Bernard, Hôpital Saint-Louis, Paris. In addition to complete clinical examination with measurement of tumor masses, the evaluation included biological tests of inflammation and liver function, chest roentgenograms with anteroposterior and lateral chest tomograms, bilateral pedal lymphangiograms, and bone marrow biopsy from the posterior superior iliac spine. All lymph node and bone marrow biopsies were reviewed by the hospital's pathologists and classified histologically according to the classification of Lukes and Butler as modified by Rye [14].

Bone marrow biopsies were considered positive when structural abnormalities (fibrosis, necrosis) and infiltration with lymphoid or plasma cells or with typical Sternberg-Reed cells were seen. Other criteria for positivity were biopsy specimens containing large mononuclear cells with a nuclear appearance resembling that of the Sternberg-Reed cell, or typical Sternberg-Reed cells in lymph node biopsy specimens. The criteria and anatomical staging are those defined and accepted at the Ann Arbor conference [13, 19]. In addition to the presence (B) or absence (A) of clinical symptoms, we also took account, as previously reported [6], of the presence (b) or absence (a) of biological signs of disease activity.

Among these 1200 patients, six cases were excluded from the study because of an equivocal biopsy and 53 had initial bone marrow involvement. The incidence of initial bone marrow involvement reported in this study (4.4%) is comparable to that reported by Rosenberg [22], who found an incidence of 5% (8 cases of 155) in untreated patients. However, the incidence found in this study is considerably lower than reported by O'Carroll [17] and Myers [16], who found incidences of 14% and 11%, respectively.

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Results

1. Age and Sex

In contrast to the overall sex ratio, there was a disproportionately high number of male patients, with 40 men as against 13 women. Age distribution for the male population did not reveal the usual two peaks for young and middle-aged patients (Table 1).

In this series, the male-to-female ratio (40/53 patients, i.e., 75%) was slightly higher than that reported in other series with or without bone marrow involvement [12, 20, 22, 23], in which the ratio ranges from 60% to 70%. The mean age at the time of diagnosis (36 years) was higher than that of patients without initial bone marrow involvement, as pointed out by Weiss [27] and Rosenberg, who found the peak incidence to be situated during the third decade of life.

2. Presenting Symptom

In almost half our cases (26 patients) the presenting symptom was superficial lymphadenopathy, while in 31% of patients (17 cases) it was a febrile syndrome. It is noteworthy that for our general patient population, fever was the presenting symptom in only 9% of cases. The site of initial lymph node enlargement did not differ from that seen in other stages except for a higher incidence of left cervical nodes (11 cases).

It should be noted that four patients did not have superficial lymphadenopathy at the time of diagnosis and that in one patient a bone marrow biopsy performed because of lasting fever of unexplained origin was the only site of Hodgkin's disease.

Table 1. Distribution of the 53 patients

Sex M/F 40/13		Ratio = 3.07	
Age (M/F)			
20	6/3	17%	100%
20–35	17/3	38%	
35–50	10/1	21%	
50	10/3	24%	
Mean 36			
Clinical and biological stage			
Aa	1	2%	100%
Ab	3	6%	
Ba	4	8%	
Bb	45	84%	
Anatomical stage			
0	1	2%	100%
I	4	7%	
II	3	6%	
IIc	1	2%	
III	33	62%	
IIIc	3	6%	
IV	8	15%	
Histologic type			
I (LP)	2	4%	100%
II (NS)	19	39%	
III (MC)	19	39%	
IV (LD)	9	18%	
Unknown	4		

3. Anatomical Extension

If bone marrow involvement is excluded from anatomical staging, most patients had diffuse lymphoid or visceral involvement (Table 1). However, one patient had stage 0 disease, i.e., no superficial or deep lymphadenopathy. There were also four stage I patients, two of whom had no superficial lymph node involvement while one had isolated splenomegaly. This local extension, previously reported by Weiss, differs notably from the conclusions of Bennet [1]. The rest of the patient population included three stage II patients, one stage IIc with contiguous lung involvement, 33 stage III and three stage IIIc patients with pericardial involvement in one of these cases and pulmonary lesions in the two others, eight stage IV, six of whom had liver involvement (documented by biopsy in three cases, while in the other three cases involvement of the liver was confirmed by marked clinical hepatomegaly, increased serum levels of bilirubin, alkaline phosphatase, and transaminases, a liver scan showing hepatomegaly with fixation defects that regressed on treatment, distant lung involvement in one case and a vertebral lesion in one case, possibly related to an adjacent lymphangiographic lesion). It is noteworthy that splenomegaly was found in 50% of cases.

Nineteen of the 33 stage III patients had splenomegaly, and in six cases this was the only manifestation of disease below the diaphragm. Rosenberg has previously drawn attention to this high incidence of splenomegaly. Similarly, a clinically enlarged spleen was present in six of the eight stage IV patients, five of whom also had liver involvement. Hepatomegaly, not classified as specific owing to the absence of liver biopsy, was present in 12 of the 33 stage III patients. Thus, Hodgkin's disease with bone marrow involvement is associated with splenomegaly and even hepatomegaly more often than other forms of the disease. This is consistent with hematogenous spread.

4. Clinical Symptoms

Only four patients exhibited no clinical symptoms (Table 1). Of the 49 remaining patients, 45 had fever at

the time of the initial work-up. This is consistent with the findings of Weiss. Weight loss exceeding 10% of the total body weight was found in 33 patients and nocturnal sweats in 32. Ten of the 45 patients with biological evidence of active disease complained of diffuse pruritus, whereas this symptom was never noted in patients without biological evidence of active disease.

5. *Biological Signs*

The majority of patients (45 cases) had biological evidence of active disease but a complete biological work-up was not performed in all cases. The erythrocyte sedimentation rate exceeded 100 mm after 1 h in 24 patients (i.e., 45%). Other biological signs of inflammation were common, with fibrinogen levels of 600 mg/100 ml or over in 27 patients, three of whom had a level above 1000 mg/100 ml, and abnormally low serum iron in 75% of patients, with a level of less than 35 μg/100 ml in one-third of cases. Elevated levels of α2- and γ-globulins were also observed in the majority of cases. Serum albumin was always low, 80% of patients having less than 3.5 g/100 ml and 22% having less than 2.5 g/100 ml.

6. *Blood Picture*

Of the 53 patients, 49 had a blood count performed in the Department, and only these figures will be taken into account.

Hemoglobin. Forty patients (i.e., 81%) had a hemoglobin level of 12 g/100 ml or less: 11 had less than 8 g/100 ml, and extremely severe anemia ($\leq$ 6 g/100 ml) was observed in four cases (8%). The severity of this anemia was emphasized as early as 1973 by Myers [15].

White Blood Cells. The white blood cell count did not exceed 4,000/mm^3 in 29% of patients, six of whom had less than 2,000 WBC/mm^3. The majority of patients, however, had between 4,000 and 8,000 WBC (21 cases, i e., 53%). Leukocytosis, a common finding in Hodgkin's disease, was present in only 14% of cases (seven patients had over 12,000 WBC/mm^3 and two of these had over 20,000). The differential white count was usually normal but polymorphonuclear leukocytosis was seen in some cases. However, neutropenia was also encountered, particularly in leukopenic patients: of the 14 patients who had less than 4,000 WBC/mm^3, eight had less than 60% neutrophils and five had less than 50%.

Platelets. Thrombocytopenia below 150,000/mm^3 was observed in 16 patients (33%), six of whom had less than 60,000 platelets/mm^3. Abnormalities affecting several cell lines were quite common: 22 patients (45%) had cytopenia of at least two cell lines (hemoglobin $<$ 12 g/100 ml, WBC $<$ 4,000/mm^3, platelets $<$ 150,000/mm^3). This cytopenia was far more severe than in other stages of the disease. For example, Rosenberg reported only one case of leukopenia in 60 patients, and no cases of thrombocytopenia. Levinson reported similar findings [12]. These authors never found pancytopenia in the absence of bone marrow involvement, whereas in stage IV BM, there were eight cases of pancytopenia (16%) in our series and three out of 13 cases (23%) in a series reported by Weiss. According to the report of Myers, in contrast, this cytopenia did not influence the remission rate.

7. *Histology*

Four patients had no previous lymph node biopsy and no nodes amenable to biopsy. In these patients the diagnosis was established on the basis of the bone marrow specimen and the histological type could not be determined. The 49 remaining patients were distributed as follows (Table 1): two patients had lymphocyte predominance (type I), 19 had nodular sclerosis (type II), 19 had mixed cellularity (type III), two of whom had vascular involvement, and nine had lymphocyte depletion (type IV).

This distribution differs noticeably from that of other untreated cases of Hodgkin's disease seen in this Department during the same period: type I 14%, type II 44%, type III 36%, and type IV 6%. Thus, there is a higher incidence of type III and, particularly, of type IV among patients with bone marrow involvement. These findings are consistent with those of Weiss but differ from the results reported by Keller [9] and particularly Kadin [8], who observed a predominance of nodular sclerosis. Contrary to the report of Myers [16], patients with lymphocyte depletion had a poor prognosis in our series, since four out of nine such patients did not achieve remission and two patients who did achieve remission relapsed rapidly and died. The lymphocyte-predominant type is rare, and O'Carroll did not find a single case among 15 patients. Two lymph node biopsies of 49 revealed vascular involvement, an identical incidence to that reported by Kirschner [10], who found 4.4%, but this did not appear to influence the course of the disease.

8. *Bone Marrow Biopsy*

Like most investigators [16, 17, 22], we found typical Sternberg-Reed cells in the marrow of most of our pa-

tients (42 cases, i.e., 80%). However, Lee [11] reported an extremely low incidence of these cells in bone marrow biopsy specimens classified as abnormal. In 26 of our cases there was extensive bone marrow involvement, 24 patients presenting a diffuse picture and two patients a nodular picture (one or two specific nodules in the biopsy specimen). O'Carroll and Myers reported similar findings. This nodular appearance was also present in four of eleven cases without Sternberg-Reed cells. Vascular involvement was seen in one patient whose course was identical to that of the others.

Hyperplasia affecting all cell lines was observed in six cases, while in seven cases hyperplasia affected only one cell line (four erythroblastic, two granulocytic and one platelet). Hypoplasia was observed in 13 cases, affecting all cell lines and showing no correlation with peripheral cytopenia or possible bone marrow fibrosis. The latter is a common occurrence [21, 24, 26] and was encountered in 27 of our patients (50%). Collagen fibers were encountered more often than reticulin fibers. Granulomatous lesions were not uncommon, as reported by certain authors [7, 18], and we observed such lesions in marrow biopsy specimens from 11 patients. However, these lesions are not a specific feature, since they were also encountered in otherwise normal bone marrow biopsies.

Treatment

Since the patients in this study cover a 12-year period, treatment was not always the same. Forty-eight patients of 53 were treated with: six monthly cycles of MOPP [2] (35 cases) or according to protocol H6-67 [5] (8 cases; this consists of six weekly courses of: on day 1 vincristine 6 mg/m^2 IV, thiotepa 6 mg/m^2 IV, rufocromomycin 60 μg/m^2 IV and from days 1 through 7, methylhydrazine 100 mg/m^2 PO and prednisone 40 mg/m^2 PO, followed by maintenance treatment with methylhydrazine and chlorambucil for 3 years) or protocol CVPP (4 cases). Protocol CVPP consists of six monthly cycles of the following combination: vinblastine 4 mg/m^2 IV on days 1 and 8, CCNU 75 mg/m^2 PO on day 1, methylhydrazine 100 mg/m^2 PO and prednisone 40 mg/m^2 PO from days 1 through 14 followed by maintenance treatment with chlorambucil for 3 years. In 1971, one patient went into shock following the first infusion of MOPP and subsequently received vinblastine alone (10 mg twice a month). Among the five remaining patients, one died before treatment could be initiated, and four treated as outpatients were lost to follow-up early in the treatment.

1. Tolerance

Combined chemotherapy was generally well tolerated, though 11 patients suffered hematologic toxicity affecting at least two cell lines and requiring a reduction of dosage to at least half the initial dosage. Whereas the initial blood count did not appear to influence hematologic tolerance to chemotherapy, marrow fibrosis was an important factor since it was present in 10 of the 11 patients who subsequently suffered severe hematologic toxicity.

2. Results of Induction

Of the 48 patients, 39 achieved remission (82%). Of these 39 patients, 44% had a complete response (CR) and 38% had a partial response (PR). Most of the partial responders had superficial or deep lymphadenopathy that did not regress completely. Half the patients treated according to protocol H2-65 showed a complete response (18/35), as did three of the four patients treated according to CVPP. In contrast, no complete responses were seen among patients on protocol H6-67. Two patients died during induction with MOPP after one and three cycles respectively. The first patient exhibited no remarkable features but the second patient had vascular involvement on pathologic examination of a lymph node, which revealed a type IV histologic appearance. The four patients who progressed on treatment all had extensive disease with visceral involvement in three cases. One of these patients, who had persisting bone marrow involvement after four cycles of MOPP, was put on protocol H6-67 and subsequently had a normal bone marrow biopsy though mediastinal lymph nodes failed to regress completely. Of the three patients in whom 'no change' (less than 50% regression of tumor masses) was recorded, two became worse while the third patient received radiotherapy above and below the diaphragm (including the hilum of the spleen and liver) in a tumor dose of 2500 rad. This patient achieved complete remission of celiac and hepatic lesions previously documented during a laparotomy in the course of which splenectomy was performed.

These results are comparable to those reported by Myers, who obtained 75% complete responses, and are better than those of Weiss who recorded only a 54% response rate (CR + PR). These figures are comparable to those observed for other forms of visceral involvement [3, 6].

3. Postinduction Treatment

Reinduction every 3 months for the first year and then every 6 months was performed without randomization in 18 patients who achieved remission (12 CR and 6 PR). Large-field irradiation complemented induction therapy in seven patients (4 CR and 3 PR). Mainte-

nance treatment with vinblastine and reinduction were anticipated for a mean period of 4 years. Nine patients are currently in complete remission and have had no treatment for periods ranging from 1 to 6 years.

4. Changes in Bone Marrow Tissue

A second bone marrow biopsy specimen (usually from the contralateral posterior superior iliac spine) was obtained to confirm the response. Preexisting collagen or reticulin fibrosis disappeared completely.

Viola [25] and Myers also observed disappearance of fibrosis. Myers, however, noted regular disappearance of predominantly reticulin fibrosis, whereas this occurred in only three of six cases of predominantly collagen fibrosis despite complete remission. Moreover, this author observed normal myelopoiesis in some cases, whereas in our series virtually all biopsy specimens obtained from patients who achieved remission showed marrow hypoplasia.

Recurrence

Among the 40 patients who achieved remission (including the patient who initially failed on MOPP and subsequently achieved a PR on protocol H6-67), 14 relapsed. As in the study by Myers, most of our recurrences (11/14) occurred during the first year. One patient was excluded from the long-term results since this patient was lost to follow-up a few months after six cycles of MOPP, which produced a remission, and was seen again in the department only a year later, by which time there was recurrence in the lung, liver, and probably bone marrow. Duration of remission was therefore evaluated in 39 patients. Among the 21 patients who achieved complete response, only three had a recurrence, as against 11 of the 18 patients who achieved partial response. Only one recurrence was seen among the seven patients who received large-field preventive radiotherapy, and this recurrence was in a nonirradiated area. Among the 18 patients who had reinduction by combined chemotherapy, four relapsed (1 CR and 3 PR) (Table 2).

Site

The extent of recurrence and its site as compared to initial involvement are of considerable importance (Table 3). Indeed, four patients had a local recurrence (stage IA) and all achieved CR after complementary radiotherapy. These recurrences were all in the area most affected initially. In contrast, the other ten patients all had a visceral recurrence (including 5 in liver and 3 in bone marrow), which was always fatal within a few months despite intensive therapy. In nine of these ten cases, the first signs of recurrence were in the lymph nodes initially most affected. Another patient who had liver involvement before initiation of treatment had a recurrence in this same organ. Two patients, however, had a recurrence in a visceral organ (vertebra, liver) that was initially uninvolved and with no involvement of neighboring organs. Lastly, isolated bone marrow involvement characterized two other recurrences. In all patients but three, recurrence was observed during the first year, as shown on the remission curve (Fig. 1), which also demonstrates the importance of achieving a complete remission. One of the other three patients had a recurrence after five years. Recurrence in this patient was open to question since following the initial response she had a right mediastinal mass that remained unchanged throughout the course of her disease. After 5 years, the persistence of this lymphadenopathy and biological signs reflecting disease activity led to classification as a recurrence and she received mantle irradiation, which had little effect on the mediastinal mass. She has

Table 2. Postinduction treatment and recurrences

Results of induction	Postinduction treatment				Total
	Maintenance	Maintenance and reinduction	Maintenance and radiotherapy	Maintenance and reinduction and radiotherapy	
CR	5 (2)	12 (1)	4 (0)	–	21 (3)
PR	19 (8)	6 (2)	2 (0)	1 (1)	18 (11)
Total	24 (10)	18 (3)	6 (0)	1 (1)	39 (14)

Figures in parentheses indicate numbers of recurrences

Table 3. Site and extent of recurrence related to initial involvement

No.	Age	Sex	Initial lymphoid extension	Initial involvement	Type of remission (protocol)	Complementary treatment	Interval remission → recurrence (months)	Initial site	Extent	Treatment	Results
1	22	♂	IIc	R. mediast. R. lung	PR (MOPP)	Maint	12	R. mediast. R. lung	Ic Ab	Rx	CR
2	28	♀	III	Bilat. mediast. Liver	PR (H6–67)	Maint	61	R. mediast	I Ab	MOPP + Rx	CR
3	32	♂	III	R. supclav. Bilat. mediast. Liver	PR (H6–67)	Maint	1	R. supclav. Bilat. mediast.	IV Bb	Rx + chemotherapy	Dead
4	18	♀	III	L. cervical Lymphang.	PR (MOPP)	Maint	3	Liver	IV BM Bb	–	Dead
5	23	♂	III	L. cervical Bilat. mediast. Spleen, Liver	CR (MOPP)	Maint	8	Bilat. mediast. Liver	IV Bb	Chemotherapy	Dead
6	17	♂	III	Bilat. mediast Spleen	PR (MOPP)	Maint + Ri	3	L. mediast.	I Aa	Rx	CR
7	36	♂	III	Bilat. supclav. Ant. mediast. Lymphang.	PR (MOPP)	Maint + Ri	44	Marrow	IV BM Ab	Chemotherapy	Dead
8	29	♂	III	R. cervical Spleen Lymphang.	CR (MOPP)	Maint +Ri	4	Vertebra (T4–T5)	IV Bb	Rx + chemotherapy	Dead
9	52	♂	II	L. cervical R. supclav.	PR (Velban)	Maint	1	Liver	IV Bb	–	Dead
10	46	♂	I	Lymphang. (adjacent to L3)	CR	Maint	9	Vertebra (L3)	IV Aa	Rx	Dead (suicide)
11	19	♂	III	L. supclav. Ant. mediast. Lymphang.	PR	Maint + Ri + Rx (mantle)	40	Spleen Splenichilum Lateroaortic	I Aa	Rx	CR
12	57	♂	III	Diffuse lymphang.	PR	Maint	8	Paraverte- bral (lumbar)	IV Bb	RX + chemotherapy	Dead
13	23	♀	III	Bilat. cervical and supclav. Diffuse mediast.	PR	Maint	12	Liver, Pancytopenia	IV BM Bb	–	Dead
14	17	♀	I	Ant. mediast.	PR	Maint	3	Marrow	IV BM Bb	Chemotherapy	Dead

R = Right; L = Left; Supclav. = Supraclavicular; Bilat. = Bilateral; Rx = Radiotherapy; Mediast. = Mediastinum; Ant. = Anterior; Lymphang. = Lymphangiogram; Maint = Maintenance; Ri = Reinduction

now been without treatment for 1 year. Thus, if this special case is excluded, half the patients who achieved remission have a follow-up exceeding 7 years and none has had a recurrence after 4 years of remission.

This recurrence pattern suggests the usefulness of complementary irradiation once remission has been achieved, because of the rapidity and site of recurrence, as advocated as early as 1973 by Frei [4]. However, results differed according to whether the remission obtained was complete or partial. Only three of 21 patients who achieved complete remission subsequently relapsed, as against 11 of 18 with partial remissions ($P < 0.01$). Furthermore, only one recurrence was observed among 12 patients in CR who received reinduction chemother-

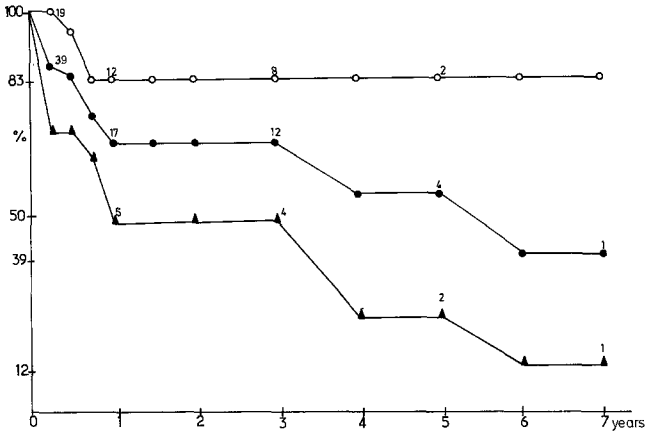

Fig. 1. Remissions achieved in Hodgkin's disease (stage IV with bone marrow involvement). O—O, CR (complete response: 21 cases); ▲—▲, PR (partial response: 18 cases); ●—●, total number of responders (CR + PR: 39 cases)

apy. Complementary radiotherapy therefore appears mandatory if CR has not been achieved, and only one failure was observed. Second-line chemotherapy has little chance of producing CR, whence the necessity of undertaking radiotherapy without delay if other lesions persist once the marrow has been sterilized. Irradiation should be performed before the usual six monthly cycles have been completed, since if a CR is going to be obtained, it is usually observed after three or four cycles. In patients achieving CR, reinduction lowers the recurrence rate to less than 10% (1/12, as against 2/9 for patients on maintenance therapy) but the difference is not significant. Moreover, none of the seven patients treated with complementary radiotherapy had a recurrence (except for one below the diaphragm immediately after mantle irradiation). Radiotherapy therefore appears to be less justified in patients achieving a CR, but in view of the recurrence pattern of patients exhibiting only a PR, it may be wise to combine radiotherapy with systematic reinduction, which we have previously shown to be advantageous in cases of visceral involvement [6].

Our long-term results are considerably better than those of Weiss and those of Rosenberg, probably because of the addition of complementary treatment. They are comparable to those of Myers, who observed a CR rate of 49% at 4 years as against 54% for all our remissions. When only cases of CR are considered, the curve shows a plateau at 83% after the first year, with a maximum follow-up of 7 years.

Survival

As mentioned earlier, two patients died during induction therapy with MOPP. Of the seven initial failures, two achieved subsequent remission, one on a new chemotherapy regimen and the other with irradiation above and below the diaphragm after failure of three cycles of CVPP. The other five failures had a very short survival, as did the ten cases of extensive recurrence already studied. The actuarial survival curve (Fig. 2) shows that no deaths have been recorded among the 15 patients in whom follow-up exceeds 3 years. The survival rate remains at 57% with a maximum follow-up of 9 years. Weiss reported a median survival of 9 months, Rosenberg found 70% survival at 30 months, and Myers 70% at 4 years. The survival curve for our patients plateaus at 57% beyond the third year with a maximum follow-up of 9 years, but our CR rate is lower than that of other groups.

Conclusion

Complementary radiotherapy therefore appears to be indispensable if only partial remission is obtained, and it should be undertaken as soon as chemotherapy has been terminated, since recurrence tends to be early. Radiotherapy may also be considered even in patients achieving CR, since the mode of recurrence is the same, although the addition of reinduction therapy reduces (but not significantly) the risk of recurrence. The areas irradiated should be those most affected initially, and if

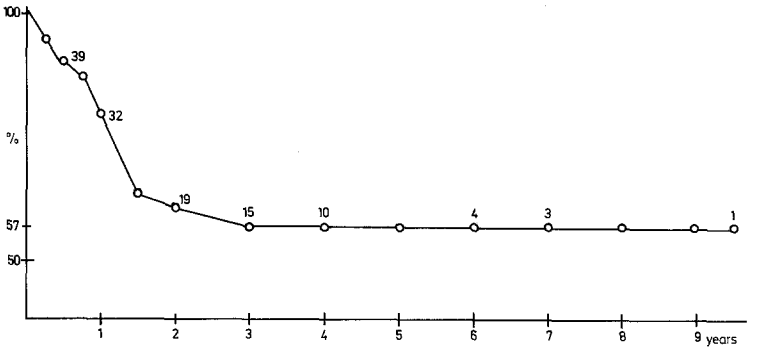

Fig. 2. Survival curve for 48 treated cases of Hodgkin's disease (stage IV with bone marrow involvement)

the disease is not too extensive, neighboring areas should also be irradiated. Two problems arise however: (1) In cases of extensive disease, should diffuse irradiation above and below the diaphragm be performed, thus precluding the possibility of subsequent chemotherapy in case of recurrence? (2) Should the tumor dose be as high (4000 to 4500 rad) as in patients receiving no chemotherapy prior to irradiation?

A number of protocols have been designed and tests are in progress with tumor doses of 2500 rad, which are believed to be sufficient because of the reduction of tumor masses by chemotherapy. Such doses allow irradiation of a larger number of areas. However, the successive application of these two techniques (radiotherapy and reinduction) should further improve long-term results, while the alternation of two or three combined chemotherapy regimens for induction should increase the complete response rate.

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