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LONG-TERM RESULTS OF TREATMENT OF CHILDHOOD AND ADOLESCENT HODGKIN'S DISEASE IN 73 PATIENTS: THE EXPERIENCE OF THE DEPARTMENTS OF RADIOLOGY AND HEMATOLOGY OF THE UNIVERSITY OF ROME "LA SAPIENZA"

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ABSTRACT

Purpose. **Various experiences show no substantial differences between children and adults in the treatment of Hodgkin's disease. In consideration of some peculiar characteristics of these cases which might influence the therapeutical choice, particularly regarding long-term survival and therapeutical complications, we report the results of a series of 73 children and adolescents with Hodgkin's disease treated at the University of Rome "La Sapienza".**

Methods. **Between 1976 and 1983, 73 untreated pediatric cases of stage I-IV Hodgkin's disease were treated with radiotherapy, alone or associated with chemotherapy, using high doses and extended fields.**

Results. **Fifty-six patients (77%) were in continuous complete remission in April 1995 and seventeen (23%) had died.**

Conclusions. **The authors confirm the excellent results in the treatment of pediatric Hodgkin's disease, both in terms of overall and relapse free survival, in spite of a high incidence of complications caused by the aggressive treatment used in this series. Therefore the majority of authors suggest combined alternating low-dose radiation administered with small portals and short-term chemotherapy. These procedures provide optimal results together with a significant reduction of complications. Consequently, it is very important to evaluate all patient characteristics accurately in order to tailor optimal treatment and select cases with risk factors which might be undertreated and therefore undergo a higher risk of recurrence.**

Key words: Hodgkin's disease, children, radiotherapy, chemotherapy, long-term survival

Between 1976 and 1983, children and adults presenting Hodgkin's disease (HD) were submitted to the same treatment at the Departments of Hematology and Radiology of the University "La Sapienza" of Rome. After pathological staging, asymptomatic non-bulky early stages were submitted only to radiation therapy (RT) with extended fields. After clinical staging, cases with symptomatic, bulky or advanced stage were submitted to curative chemotherapy (CT) followed by maintenance radiation.

Several studies have reported an important increase in complications and morbidity in children with respect to adults when laparotomy with splenectomy, curative polychemotherapy and curative extended field radiotherapy were employed.[1,2]

We report the consequences of an aggressive therapeutic approach after a long follow-up of 73 pediatric Hodgkin's disease patients, in order to evaluate whether these complications might influence long-term results by impairing survival and quality of life.

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Patients and Methods

Staging procedures

Between January 1976 and September 1983, 73 consecutive untreated HD patients less than 20 years of age were treated at the Departments of Hematology and Radiology of the University "La Sapienza" of Rome. Histology was graded according to the Lukes and Buttler criteria and staging according to the Ann Arbor classification.[3,4] Clinical staging consisted of careful physical examination, blood counts, chest X-ray, mediastinal tomography, bipedial lymphangiography, bilateral bone marrow biopsy and, from 1979 on, CT of the chest and abdomen. Skeletal X-rays and 99Tc bone scan were performed only in selected cases. Bulky disease was defined as a superficial mass greater than 5 cm in max. diameter, or a palpable abdominal mass, or a mediastinal mass occupying more than 1/3 of the maximal transverse chest diameter.

Pathologic staging, employed routinely in all asymptomatic children in early stage (except those under 6 years), consisted of laparotomy with splenectomy, left and right liver lobe biopsy and biopsies of all detectable lymph nodes. From 1982, prophylactic penicillin and polyvalent pneumococcal vaccination were administered to splenectomized patients, along with complete blood cell count, ESR, liver and renal function tests. Data concerning the age, sex, histology and stage of patients are summarized in Table 1.

There were 41 males and 32 females, with a median age at diagnosis of 16 years (range 6-20). The histologic subtypes included 27 cases of nodular sclerosis, 26 of mixed cellularity, 10 of lymphocyte predominant, 6 cases of lymphocyte depletion, and 4 patients could not be evaluated for histological subtype. Ten patients were in stage I, 16 were in stage II, 36 in stage III and 11 in stage IV. Pathological staging was performed in 18 patients, while 55 were only clinically staged. Thirty-eight out of the 55 pts initially only clinically staged were later submitted to restaging laparotomy in order to evaluate the results of treatment.

Treatment plan

Eighteen patients with pathological stage I-II A (non-bulky) received extended field (EF) radiotherapy alone, with a total dose of 36-44 Gy delivered by a 6 MeV linear accelerator or 60Cobalt unit. This consisted of mantle field irradiation. Fifty-five patients with symptomatic early stage (I-IIB), IIA bulky and advanced stage (III-IV) were randomized to receive 6 cycles of MOPP versus 6 courses of ABVD; Thirty-five patients received MOPP and 20 were treated with ABVD. All 42 cases who achieved complete remission after chemotherapy were submitted to maintenance therapy, which was tailored according to the initial stage of the disease. This consisted of mantle or inverted "Y" field radiotherapy for stage I-IIB and IIA bulky, of mantle plus inverted "Y" field for stage III, and of polychemotherapy according to the PROVECIP regimen (procarbazine, vinblastine, cyclophos-

Table 1. Patient characteristics.

	MOPP	*ABVD*	*RT*	*TOTAL*
Patients	35	20	18	73
Sex				
Male	16	16	9	41
Female	19	4	9	32
Symptoms				
A	21	9	18	46
B	14	11	-	27
Stage				
I	-	1	9	10
II	5	2	9	16
III	23	13	-	36
IV	7	4	-	11
Age				
Median	16	14	17	16
Range	6 - 20	6 - 20	(8-19)	6 - 20
Histology*				
NS	9	9	9	27
MC	17	5	4	26
LP	5	2	3	10
LD	2	2	2	6
not evaluable	2	2	-	4
ESR <40	7	2	8	17
ESR >40	28	18	10	56

** NS=nodular sclerosis; MC=mixed cellularity; LP=lymphocyte predominant; LD=lymphocyte depletion.*

phamide and prednisone)[5] for stage IV. Radiotherapy was delivered by a 6 MeV linear accelerator for a total dose of 30-36 Gy.

The results of treatment were defined as follows:

– complete remission (CR): complete disappearance of all signs and symptoms of disease;
– partial remission (PR): reduction of at least 75% of initial signs of disease;
– failure to respond to treatment: resistant or progressive disease.

Follow-up

Patients were followed-up with chest X-rays, blood counts and physical examination every 3 months for the first 2 years, every 4 months for the next 3 years and every 6 months thereafter. Patients also had a total body CT scan after 1979, and thyroid function tests were run every 12 months for the first 5 years. Follow-up for the entire study population ranged from 6 to 19 years.

Statistical analysis

Overall survival was calculated from diagnosis to last follow-up. Relapse free survival (RFS) was estimated from CR to the possible appearance of relapse or last follow-up. Continuous complete remission (CCR) was calculated from the date of complete remission to last follow-up.

Actuarial 120-month survival and (RFS) figures were calculated using the method of Kaplan and Meier.[6] Statistical significance was evaluated with the log-rank test. Contingency table chi-square tests were used to evaluate treatment differences in response patterns.[7]

Results

Table 2 shows the results of therapy according to the different treatment schedules.

In the group of 18 patients treated with EF radiotherapy we observed 3 relapses, 15, 38, and 46 months after CR, and 4 deaths (one in CR of meningococcal infection and two of progressive disease; the last one died of a second malignancy 155 months from diagnosis).

Fourteen patients are presently in continuous complete remission with a median follow-up of 151 months (range 73-199). The probability of 10-year CCR was 77%, while both RFS and overall survival were 81% at 10 years (Figures 1 and 2).

Table 2. Response to treatment.

	RT	*%*	*MOPP*	*%*	*ABVD*	*%*	*TOT*
Patients	18		35		20		73
C.R.	16	(89)	27	(77)	15	(75)	58
Failure	2	(11)	8	(23)	5	(25)	15
Relapse	3	(17)	7	(20)	2	(10)	12
Death	4	(23)	6	(17)	7	(35)	17

Twenty-seven out of the 35 cases treated with MOPP achieved CR; they were subsequently submitted to consolidation radiotherapy (23 patients) or chemotherapy (4 patients). The other 8 patients treated with MOPP failed to respond. Five of them received salvage chemotherapy, while the other 3 were treated with radiotherapy. Five died of progressive disease; one, who achieved CR, relapsed after 33 months and died of progressive disease. The last two achieved CR and are alive at the time of this study.

Six out of the 27 cases treated with MOPP who achieved CR relapsed after 18, 30, 31, 62, 79 and 117 months. All of them achieved a second CR with salvage chemotherapy (ABVD) or radiotherapy (1 case). Twenty-nine patients are in CCR with a median follow-up of 156 months (range 111-219). The probability of 10-year CCR was 83%, that of RFS and overall survival was 75% and 88%, respectively (Figures 1 and 2).

Overall survival and RFS in this group according to the different maintenance therapies, were 87% and 76% in the RT-group, 88% and 73% in the CT-group, respectively.

Fifteen out of the 20 cases treated with ABVD achieved CR and were submitted to maintenance radiotherapy (12 patients) or chemotherapy (3 patients). The other 5 patients did not respond to therapy and received salvage chemotherapy; 3 died of progressive disease and the other two achieved CR, but one died of cardiac

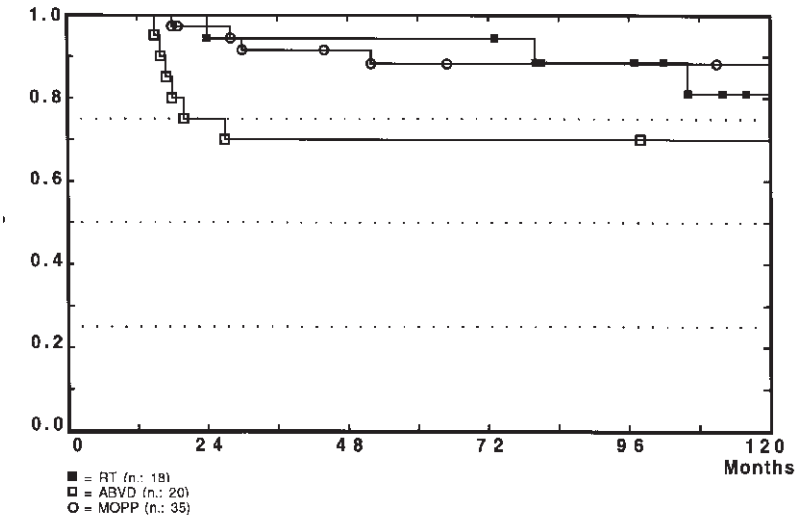

Figure 1. Overall survival of the three groups.

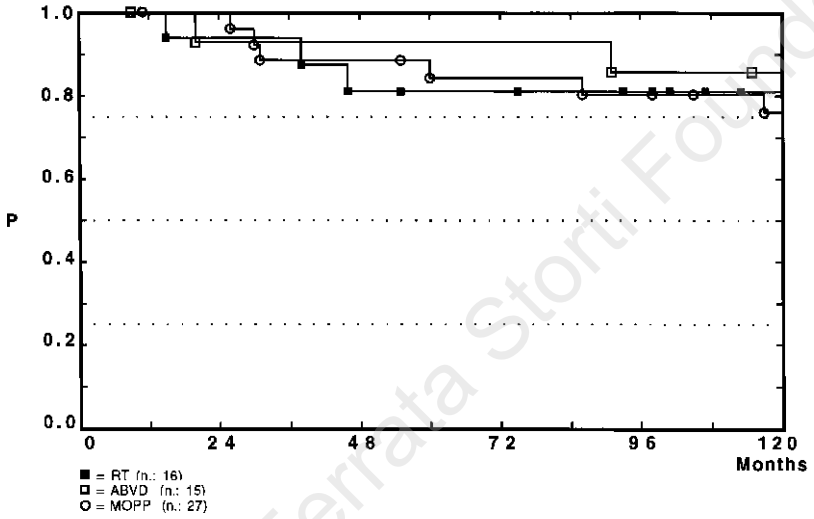

Figure 2. Disease free survival of the three groups.

complications. Two out of the 15 patients treated with ABVD and in CR died of complications: the first of a non-Hodgkin's lymphoma (NHL), the second of a viral infection at 127 and 9 months, respectively, from the completion of therapy. Two other cases relapsed after 21 and 91 months; the first achieved a second CR with salvage chemotherapy, while the other refused further therapy and died of progressive disease. Thirteen patients are in CCR at a median follow-up of 154 months (range 123-228). The probability of CCR at 10 years was 65%, of RFS and overall survival 85% and 70%, respectively (Figures 1 and 2).

Overall survival and RFS for this group according to the different maintenance therapies were, respectively, 71% and 85% in the RT group, 69% and 84% in the CT group.

Toxicity and late effects

Table 3 shows the late effects of treatment. No intra-operative death due to laparosplenectomy was observed among the 56 patients submitted to this procedure. One patient developed bacterial meningitis 8 years after the end of therapy. Excluding the 17 pts submitted to additional therapy, herpes zoster was found to be the most common infection in the remaining 56 pts

Table 3. Late effects in patients in C.R. after therapy

	MOPP	*%*	*ABVD*	*%*	*RT*	*%*	*TOT.*	*%*
Patients	25		15		16		56	
Herpes Zoster	5	(20)	2	(13)	3	(19)	10	(18)
Bact. or viral infections	5	(20)	4	(26)	6	(38)	15	(27)
Pulmonary fibrosis	2	(8)	1	(7)	3	(19)	8	(11)
Cardiac complications	–		1	(7)			1	(2)
Azoospermia*	6/11	(55)	5 / 12	(42)	1/4	(20)	12	(43)
Amenorrhea**	10/14	(71)	2 /3	(66)	1/9	(11)	13	(50)
2nd neoplasm	1°	(4)	1@	(7)	1#	(6)	3	(5)
Hypothyroidism	2/25	(8)	1/15	(7)	–/5		3/45	(7)
Growth impairments	3	(12)	5	(33)	3	(19)	11	(20)
Psychological impairments	3	(12)	5	(33)	4	(25)	12	(43)

* MOPP Tot. 11 pts, ABVD Tot. 12 pts, RT Tot. 4 pts; ** MOPP Tot. 14 pts, ABVD Tot. 3 pts, RT Tot. 9 pts; °Leiomyosarcoma; @NHL; #breast cancer.

(18%). Eleven patients (20%) showed growth impairment; 3 had received MOPP, 5 ABVD and 3 EF radiotherapy.

Three (7%) out of the 45 patients undergoing periodical thyroid function tests showed clinical signs of hypothyroidism: 2 of the 25 treated with MOPP and 1 of the 15 treated with ABVD.

Semen analysis was performed only in 23 males submitted to chemoradiotherapy: azoospermia was observed in 11 of them (48%): six (55%) out of the 11 treated with MOPP and 5 (42%) of the 12 treated with ABVD. All seven cases submitted to consolidation RT with mantle plus inverted Y field after chemotherapy showed azoospermia.

Four out of the 8 males treated with RT underwent semen analysis and only 1 (20%) of them developed azoospermia.

One (11%) out of the 9 evaluated females treated with radiotherapy alone developed amenorrhea; none of them had received pelvic irradiation. In the MOPP group, 10 (71%) out of the 14 females showed persistent amenorrhea. In the ABVD group, 2 (66%) out of the 3 evaluable females presented persistent amenorrhea. Seven females from this series, 2 treated with MOPP and 5 with RT alone, had a regular pregnancy.

Pulmonary fibrosis was observed in 2 (8%) patients treated with MOPP plus RT, in 1 (7%) case in the ABVD plus RT group, and in 3 (19%) patients treated with RT alone.

One patient treated with ABVD plus RT developed cardiac dysfunction and died of heart failure.

Another patient in the MOPP group developed a leiomyosarcoma in one of the irradiated areas and another one, submitted to RT alone, developed breast cancer 120 and 115 months, respectively, after irradiation. One case of NHL was observed 116 months after therapy in the ABVD group. No patient developed a secondary leukemia.

Four patients presented psychiatric complications during follow-up; they are still undergoing psychiatric treatment.

Eight more cases showed psychological impairment with pathological social behavior.

Statistical analysis, performed with the chi-square test, did not show any differences according to single complicance appearance in the three therapeutical regimens.

Discussion

Hodgkin's disease is relatively rare in childhood.[8] Moreover, many authors have reported peculiar aspects of the disease in younger children. These include male sex predominance and a higher incidence of localized disease. Similar to many published series, there was a male predominance in our patients with a M:F sex ratio of 1.5.[8-14]

In comparison to larger pediatric series, we observed a relatively low percentage of limited HD (stages I-IIA 24%). These findings could be related to the relatively higher median age (16 years) of our group of patients, with only 9 children under 10 years of age.

In our series the rate of nodular sclerosis and mixed cellularity histotypes were similar (37% and 36%, respectively). In other series, the rate of NS was greater than MC.[8,9,12,14,15]

Similar therapeutic results in adults and children are reported. At 10 years of follow-up, CCR rates of 75-90%, survival rates of 85-90% with corresponding DFS rates of 66-76% are reported in several pediatric series.[13-18] In our

study the CCR, overall and disease-free survival rates were 77%, 79% and 82%, respectively. In spite of a greater death rate in this series, possibly due to a higher median age, these data confirm the high curability rate of pediatric HD.

In stages I-IIA, EF radiotherapy with curative doses resulted in a 90% CR rate, 86% DSF and 81% overall survival. Our results are similar to the majority of series with patients treated with high-dose EF radiotherapy.[12,15]

High doses and large volumes of irradiation have frequently been related to growth retardation, particularly in the age of active bone growth.[19-21] In our series, all treated cases less than 10 years of age presented this late side effect.

In an attempt to reduce radiotherapy-related complications, chemotherapy associated with low-dose EF radiotherapy or high-dose IF radiotherapy was also employed in the treatment of localized HD.[13,22,23] These studies and others[19] showed a lower rate of relapse and of growth retardation compared to our group. Therefore, in comparison to our study, Schellong reported an increase of gonadal dysfunction due to the presence of procarbazine in the chemotherapy regimen utilized.[18]

With the exclusion of this drug from the therapeutic schedule gonadic complications disappeared, but the incidence of relapse reached a percentage similar to our group. However, the introduction of combined chemoradiotherapy in early stage decreased the importance of an accurate evaluation of the extension of the disease, obtained in our patients with laparosplenectomy, which is correlated with an increase in infections.[13,24-26]

Some authors report results of patients submitted to laparoscopic splenectomy; their series show interesting preliminary findings with a significant reduction of infective complications.[27-29]

In our cases undergoing surgical staging, 22% bacterial infections, early or late, were observed with one death due to late meningitis.

Oberlin observed a reduction in the percentage of infections in cases submitted to low-dose RT (< 20 Gy) without late infections and he affirmed that splenic irradiation with 20 Gy did not impair this organ's functions.[13]

Regarding data on patients submitted to prophylactic penicillin, the numbers were too small to draw conclusions regarding the efficacy of this therapy.

In advanced stage HD the use of chemoradiotherapy treatments is well documented.[2,16,18,22,30-32] Schellong and others used 6 cycles of COPP and OPPA and RT for a total dose of 25 Gy on the IF.[18] Similarly, Hudson and Mefferd in their series used 4-6 cycles of chemotherapy added to RT for a total dose of 20-25 Gy on the IF, while Weiner added 8 cycles of ABVD and MOPP alternated with EF radiotherapy for a total dose of 21 Gy.[16,22] Results in all these studies and others[30-32] range between 85-95% for overall survival and between 75 and 93% for disease free survival at 5 years. Results were similar in our series (80% total survival and 79% RFS), although 70% overall survival was observed in patients treated with ABVD versus 88% in the group treated with MOPP. However, no statistically significant difference was demonstrated in the two arms, either in terms of overall or RFS.

Several authors reported a correlation between gonadal function and the association of CT and RT.[10,33,34] Forty-eight percent of the males in our group submitted to seminal analysis developed permanent azoospermia. Schellong reported 30% azoospermia, which reached 60% with the addition of procarbazine in the chemotherapy scheme. However, in this study when IF radiotherapy was employed patients who did not undergo pelvic irradiation did not develop sterility, while Hudson reported the presence of amenorrhea in 30% of the females using a similar chemoradiotherapeutic protocol.[18,22]

In our series, 69% of the females submitted to chemoradiotherapy showed persistent amenorrhea. Compared to the data from the literature, we observed a lower percentage of lung fibrosis in our series.[11,30,35] These data, however, were acquired through seriate radiological exams and investigations, while breath tests and chest X-rays were perfomed only in patients with evident clinical symptoms.

Likewise, in this series, cardiac function tests were not performed routinely and this might explain the lower incidence of cardiac complications compared to data from the literature.[11,30,35,36]

Only one patient in this series developed symptomatic cardiac dysfunction; he had previously been treated with 6 courses of ABVD and RT. Several authors have described cardiac complications induced by the association of adriamycin with RT.[11,35,36]

The possibility of developing secondary malignancies in patients treated for Hodgkin's disease has been reported in several series in the last 20 years.[37-39] Some authors reported an excess risk of development of in-field malignancies in cases treated with radiation.[40]

In our series we observed one case of leiomyosarcoma among patients submitted to chemotherapy, and a breast cancer in a patient treated with RT alone. Because of the few cases in this study we could not calculate the actuarial risk of the appearance of secondary neoplasms. Another case out of the 40 treated with chemotherapy developed a NHL.

Some authors reported a correlation between laparosplenectomy and an increased risk of appearance of secondary leukemia.[37,38] No secondary leukemias were observed in our group in spite of a higher rate of patients submitted to laparosplenectomy. EF and high-dose RT showed an excellent percentage of overall and disease-free survival in spite of a higher morbidity. Several authors using low-dose or IF radiotherapy associated with CT obtained similar survival values together with a lower incidence of complications.

In our historical series patients were submitted to more aggressive therapy than that reported by the majority of authors. In spite of this approach our results were similar to other series, although we observed a higher incidence of complications, which might have also influenced the long-term survival.

Therefore the optimal therapy for pediatric Hodgkin's disease is an association of alternating short-term chemotherapy and intermediate or low-dose radiation with small portals. In order to prevent an increase of recurrence in possibly undertreated patients, it is very important to analyze their characteristics, particularly in early stage cases with positive risk factors, which might be at higher risk of recurrence with inadequate non aggressive therapy.

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