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Brief Chemotherapy Associated with Extended Field Radiotherapy in Hodgkin's Disease. Long-term Results in a Series of 102 Patients with Clinical Stages I–IIIA

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Abstract—*From 1972 to 1976, 102 patients with stages I–IIIA Hodgkin's disease (HD) were treated by chemotherapy with cyclophosphamide, vinblastine, procarbazine and prednisone (CVPP: two courses) associated with extended field radiotherapy. Staging included neither laparotomy nor splenectomy (clinical staging). Treatment included neither splenic irradiation nor maintenance therapy. Complete remission was achieved for 98 patients and 11 of them recurred up to 94 months after treatment. Median follow-up of this controlled study is 13 years. Disease free survival (DFS) is 87% at 6 years and 84% at 10 and 15 years. Overall survival is 77% at 10 and 74% at 15 years. Disease specific survival is better (91% at 10 and 87% at 15 years) since only 38% (10/26) deaths were due to HD. The other deaths (16/26) with no evidence of HD were due to second cancer and intercurrent disease. Prognostic analysis of DFS by log-rank test gives significance to the following factors: contiguous extra-nodal involvement (P = 0.008), more than 3 involved sites (P = 0.01), signs of compression (P = 0.02), clinical stage IIIA (P = 0.03), infradiaphragmatic stages I–II (P = 0.04). The potential risk of secondary cancer is difficult to assess.*

INTRODUCTION

In 1965, the symposia of Paris and Rye recognized the curative role of extended field radiotherapy in stages I–II Hodgkin's disease (HD) as documented by Peters [1] and Kaplan [2]. At the same time for advanced stages and for the first time, combined chemotherapy was used, especially MOPP (nitrogen mustard, vincristine, procarbazine and prednisone) as proposed by De Vita [3]. At Fondation Bergonié, early recurrences after extensive radiotherapy alone [4] led us in 1967 to introduce, for patients with poor prognosis [5, 6], chemotherapy with cyclophosphamide, vinblastine, procarbazine and prednisone (CVPP). Good tolerance [7] and good preliminary results led us in 1972 to treat all our patients with an induction course of CVPP followed by extended field radiotherapy. A consolidation course of CVPP was then given to reduce further residual disease for the purpose of a control study on the value of BCG immunotherapy [8]. This protocol was stopped in 1976 when our Institute began a new cooperative trial within the GPMC group [9]. Today with a 10 year minimal follow-up, we assess the results of this experience for patients with clinical stages I–IIIA. No surgical staging was performed during all this period. We chose to study only early clinical stages for comparison with another cooperative study [9], which began in 1976 and also studied clinical stages I–IIIA.

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PATIENTS AND METHODS

From January 1972 to October 1976, 159 new patients with HD were registered in our Institute. Fifty-seven patients were excluded from analysis for the following reasons: clinical stage IIIB or IV, 23 cases; technically unfeasible lymphangiography, two cases; clinical stages I–IIIA but with treatment already started, nine cases; refusing treatment or treated elsewhere, 23 cases. Thus, 102 patients with clinical stages I–IIIA were included in the study.

All diagnoses were established by biopsy and reviewed in our Institute. HD was confirmed and classified in all cases according to the international nomenclature [10]. Staging was established after clinical examination, bipedal lymphangiography and chest X-ray, together with mediastinal tomography. No surgical exploration was performed

and all patients were thus classified following clinical staging [11]: stage I with one lymphatic area involved; stage II with two or more lymphatic areas involved above or below the diaphragm; stage III with at least one lymphatic area involved above and below the diaphragm. Clinical staging was completed according to the data of the Rye symposium [12] with biological tests (complete blood cell count and erythrocyte sedimentation rate). It was possible to classify all patients in two groups according to data from the EORTC trial [13] which were also taken into account in the following GPMC trial [9]. The first group contained patients with a low-risk HD (group α) since they fulfilled all the following prognostic criteria: age < 40 years; pathologic type 1 or 2; clinical stage I or II with mediastinal involvement; absence of extranodal involvement (E); absence of systemic symptoms (A). The other group contained patients with a high-risk HD, because either they did not fulfil all the above favorable prognostic criteria (subgroup β) or they were stage IIIA (subgroup γ). Main patient and disease characteristics are shown in Table 1.

The CVPP chemotherapy combined four drugs: cyclophosphamide: an intravenous injection of 200 mg every other day, vinblastine: an intravenous injection of 10 mg per week, procarbazine: 6 capsules of 50 mg per day, after an initial increment of one capsule a day over the first 6 days, prednisolone: a daily injection of 120 mg per day for 3 days, then 80 mg per day for 3 other days, and 40 mg per day for the 3 last days. Each drug dosages were usually the same for all patients and not, as in other schedules, dependent on the body surface or weight. Total drug dosages depended on the hematologic tolerance: the treatment was given for a maximum of 21 days, or until the patient's leukocyte count dropped to 2×10^9/l. However, doses were reduced

Table 1. Distribution of main characteristics and prognostic analysis according to DFS

		Distribution (102 patients)	*P* value (log-rank test)
Sex	Female	34	0.07
	Male	68	
Age	<40 years	69	0.48
	≥40 years	33	
Diagnostic delay	≤5 months	61	0.08
	>5 months	41	
Karnofsky scale	90 or 100%	66	0.56
	<90%	36	
Pathologic type*	1 or 2 (1/2)	64 (18/46)	0.70
	3 or 4 (3/4)	37 (32/5)	
Clinical stage	I–II(I/II)	86 (30/56)	0.03
	III	16	
Mediastinal involvement	Absent	67	1
	Present	35	
Stages I–II	Supradiaphragmatic	81	0.04
	Infradiaphragmatic	5	
General symptoms	A	79	0.03
	B	23	
Contiguous extra-nodal involvement	Absent	93	0.008
	Present	9	
Signs of compression	Absent	87	0.02
	Present	15	
Size of the largest tumoral mass†	<5 cm	52	0.77
	≥5 cm	38	
Number of involved areas	≤ 3	66	0.01
	>3	36	
Erythrocyte sedimentation rate	≤40 mm	56	0.49
	>40 mm	46	
Group	α	23	0.02
	β+γ (β/γ)	79 (63/16)	

*One type was unclassified owing to association of two histologic types.
†Twelve tumoral masses not measurable.

for patients over 70 years (two cases) and for children under 15 years (five cases). On the other hand, for patients with bulky tumors over 10 cm, the induction course was planned to be reinforced by another course of CVPP (one case) or 3 courses of MOPP (nine cases), whenever tumoral reduction was considered as insufficient (less than 75%). All patients were hospitalized for treatment. Surveillance was clinical, especially digestive and hematologic, with blood cell count every other day during chemotherapy and weekly during radiation.

As a rule, radiotherapy immediately followed chemotherapy, and the interval never exceeded 6 days. Radiotherapy was always given with high energy radiation (photon γ of ^{60}Co). The total dose was 40 Gy in involved regions, and 35 Gy in adjacent areas. This dose was delivered with 2 Gy per day and 5 days per week, over a period of 3.5–4 weeks. No boost was administered, except in one patient who received two induction courses of CVPP and a boost of 20 Gy by electrontherapy for a cervical mass of 17 cm. Kaplan's technique with an extended field was used. For the supradiaphragmatic mantle, the anterior field required protection for the lungs, the upper extremities of the humerus and the larynx. On the other hand, the posterior field required a 2 cm wide median shield beyond 20 Gy to prevent myelitis [14]. The fields for the mediastinum were delineated in a lying position according to the abnormal lymph nodes remaining after induction chemotherapy or the again normal lines of the mediastinum, and not to the initial involvement. For the subdiaphragmatic area, the inverted 'Y' technique was used where there were pathologic lymphographic findings, but only the paraaortic area until L5–S1 was treated where there were normal films. No splenic irradiation was performed. The supradiaphragmatic mantle and the paraaortic area were irradiated simultaneously for patients with supradiaphragmatic stages I–II, but irradiation for patients with stage IIIA was divided into two phases; inverted 'Y' then supradiaphragmatic mantle.

A rest period of 1 month was inserted between the end of irradiation and the beginning of the consolidation course of CVPP. Although the leukocyte count slightly increased during irradiation [15], chemotherapy could not be repeated for four patients because of persistent leukopenia.

No maintenance therapy was given. Thus, the overall treatment was short (about 3.5 months), except for patients with stage IIIA who received irradiation in two periods.

In cases of recurrence pathologically confirmed, patients were restaged and were given the best available treatment.

All data were collected in June 1987, so the median follow-up time is 13 years. Overall survival and duration of complete remission (CR) were calculated from the first day of treatment. The curves of overall survival and disease free survival (DFS) were established according to the Kaplan–Meier method [16]. The analysis of the main characteristics was made by comparison of DFS curves, and prognostic significance was evaluated according to the log-rank test [17].

RESULTS

Tests just before the consolidation course (1 month after irradiation) showed that CR was obtained for all patients except for four: one with progression despite treatment and three with only partial remission who relapsed shortly after and despite the consolidation course. Therefore 98 patients (97%) achieved complete remission. Figure 1 shows that overall survival is 77% at 10 and 74 at 15 years, and that disease specific survival is 91% at 10 and 87% at 15 years. Figure 2 shows that

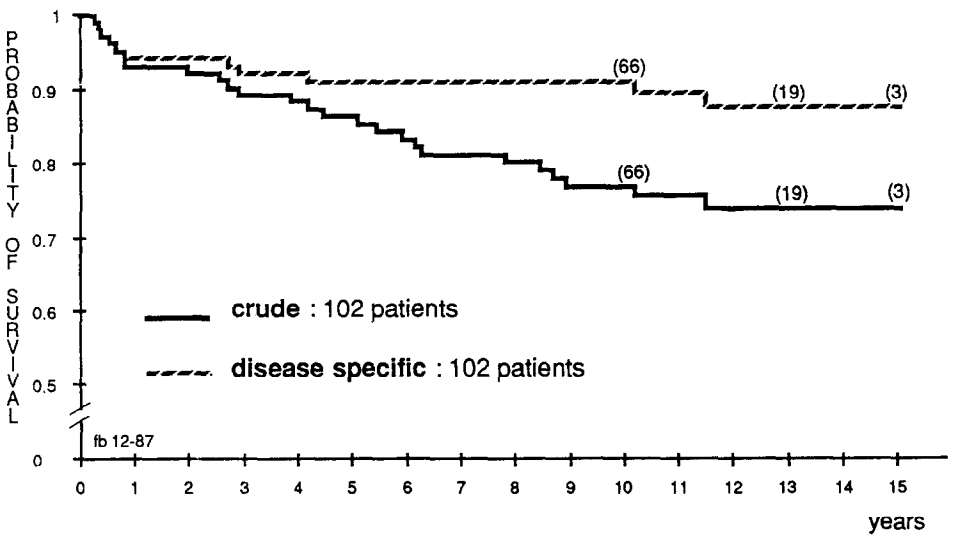

Fig. 1. Crude and disease specific survival. The numbers in parentheses indicate patients exposed to risk.

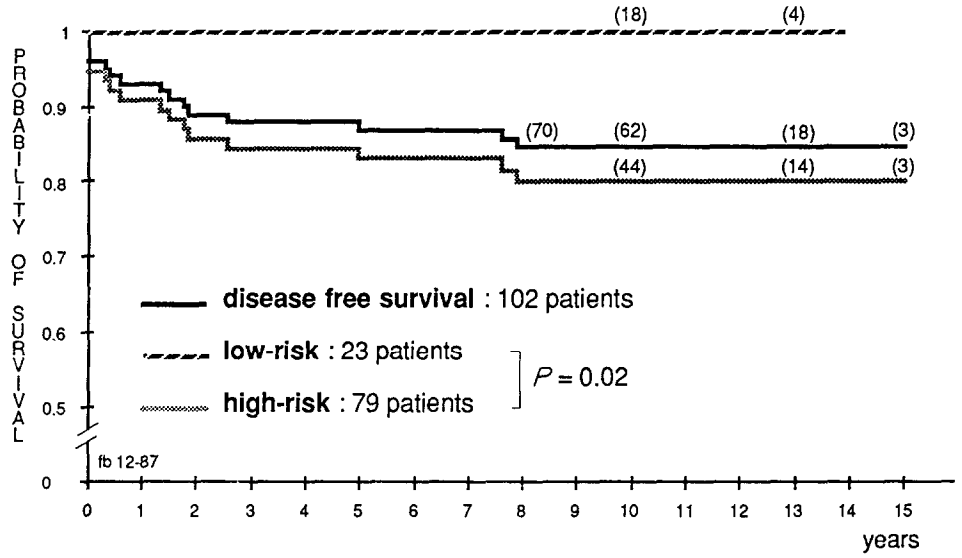

Fig. 2. Disease free survival for all patients and for patients with low-risk Hodgkin's disease (group α) vs. high-risk (group β + γ). The numbers in parentheses indicate patients exposed to risk.

disease free survival (DFS) is 84% at 10 and 15 years, since there was no recurrence beyond 94 months with 70 patients still exposed. Table 1 shows the distribution of the mean characteristics and prognostic value calculated according to the log-rank test (by comparison between DFS curves). This analysis reveals the following factors to be significant for poor prognosis: contiguous extranodal involvement ($P = 0.008$); more than three involved sites ($P = 0.01$); signs of compression ($P = 0.02$); clinical stage IIIA ($P = 0.03$); infradiaphragmatic stages I–II ($P = 0.04$). Finally, Fig. 2 shows a significant difference ($P = 0.02$) between the DFS curve of patients with a low-risk HD (group α) and that of patients with a high-risk HD (subgroup β plus γ). BCG immunotherapy gave no significant difference as previously published [8] and should be no longer considered.

There were 11 recurrences among the 98 patients who achieved CR. The disease-free duration for recurrent patients ranged from 3 to 94 months (median = 20 months). Table 2 shows the distribution according to the site of first recurrence. Recurrence is pejorative, because death occurred in nine cases, and six of these were directly due to the recurrence.

A total of 26 deaths occurred among the 102 patients. Ten were due to HD (Table 2). Indeed four patients with primary failure died quickly in the 6 months following treatment and six others died subsequent to recurrence. Among the 16 deaths with no evidence of HD, one patient died of aplasia due to the treatment, nine died of intercurrent disease and six died of secondary cancer.

Various complications occurred during follow-up (Table 2). Herpes-zoster was the most frequent infection and the three other infections were pulmonary abcess, rubella and cytomegaloviral infection. No pericarditis or respiratory insufficiency was observed, and the only specific post-irradiation complication was a case of hypothyroidism which needed a hormonal treatment. The other complications were as follows: three auto-immune thrombopenia and nine secondary cancers. Table 3 gives the characteristics of these secondary malignancies. A laryngeal carcinoma occurred in the patient who received two induction courses of CVPP and a boost of 20 Gy for a large cervical mass. The other neoplasms were three bronchial carcinomas, two non-Hodgkin's lymphomas, one osteosarcoma in an irradiated area and two cases of acute myeloblastic leukemia (one 6 years after recurrence treated by three courses of MOPP).

DISCUSSION

The results of this series depend only on the therapeutic association of chemotherapy and radiotherapy.

It is difficult to compare these results with other series which used surgical staging. Indeed, exploratory laparotomy was included in the staging system proposed at Ann Arbor in 1971 [18]. In 1965 radiotherapy alone cured half of all patients with apparently localized disease corresponding to clinical stages I–IIIA. Analysis of these failures (50%) and the discovery of occult infradiaphragmatic involvement (20–30%) after systemic laparotomy [19, 20] led the majority of authors to extend radiotherapy after surgical staging. Other teams like ours preferred to associate chemotherapy with radiotherapy. Rosenberg and Kaplan [21] have demonstrated that chemotherapy is useful even for patients who have surgical exploration and extended field irradiation. However, this maximum combined

Table 2. Distribution of sites of first recurrence, causes of death and complications

Sites of first recurrence	11	
in irradiated area (*in situ*)	3	
in marginal extension	3	
in non-irradiated area	2	
visceral or generalized	3	
Causes of death	26	
Hodgkin's disease	10	
primary failure	4	
recurrence		
failure of first recurrence	4	
failure of second recurrence	2	
Therapeutic complication (aplasia)	1	
Secondary cancer	6	2 bronchial carcinomas 1 non-Hodgkin's lymphomas 1 osteosarcoma 2 acute leukemia
Intercurrent disease	9	1 senility 1 auto-immune thrombopenia 1 varicella 1 coronary thrombosis (60 years old) 2 accident 1 suicide 2 hepatic failures
Complications	40	
Herpes-zoster	24	
Other infections	3	1 pulmonary abcess 1 rubella 1 cytomegaloviral infection
Auto-immune thrombopenia	3	
Hypothyroidism	1	
Secondary cancer	9	

treatment increases therapeutic risks. It is now known that laparotomy is not necessary for supradiaphragmatic stages IA and IIA, treated either (1) with radiotherapy alone as proposed by Griffin *et al.* [22]: supradiaphragmatic mantle plus prophylactic paraaortic and splenic irradiation (which is equivalent to splenectomy [23]), or (2) with association as proposed by Andrieu *et al.* [24, 25]: chemotherapy with MOPP (three courses) followed by supradiaphragmatic mantle irradation. With this association Andrieu *et al.* had six recurrences among 166 patients with clinical stage IA and IIA2 (A2 = 2 involved areas). Moreover, after six courses of MOPP and four courses of vinblastine, Andrieu *et al.* [25] showed that the rate of occult infradiaphragmatic involvement drops from 46 to 6%. Similarly, among 81 patients with supradiaphragmatic clinical stage I or II, we observed only one infradiaphragmatic recurrence with paraaortic involvement and one generalized recurrence with splenic and hepatic involvement. Therefore, in view of the high rate of occult infradiaphragmatic (and especially splenic) foci, it may be concluded that most of these foci were successfully treated by two courses of CVPP without splenectomy or splenic irradiation. Likewise, the necessity for systematic irradiation of the paraaortic or other adjacent areas remains debatable. Finally, patients are spared a surgical act which carries a risk of morbidity [26].

Few studies have used CVPP or similar regimen [27–29], which may be used particularly briefly and intensively. Unlike almost all chemotherapy regimens, our course of CVPP was given every day for a maximum of 21 days, or until the leukocyte count reached $2 \times 10^9/1$. No maintenance therapy was given, so the total duration of treatment was particularly brief (3.5 months) with an acceptable tolerance and apparently good efficiency. Indeed, the tolerance of this intensive treatment seems acceptable despite four cases of severe but reversible hypoplasia and one lethal aplasia.

Efficiency was also good. Although it is difficult for several reasons (surgical staging, different regimen) to compare our results with other series, the Stanford team [30] had the same DFS rate at 10 years (84%) for surgical stages I–II Hodgkin's disease treated by radiotherapy and six courses of MOPP. More interesting still is the comparison

Table 3. Characteristics of secondary cancers

	Localization	Localization in an irradiated area	Delay between treatment and secondary cancer	Status
Laryngeal carcinoma (epidermoid)	Larynx	Yes	14 years	Alive
Bronchial carcinoma (undifferentiated)	Right principal bronchus	Yes	2 years	Dead
Bronchial carcinoma (undifferentiated)	Left principal bronchus	Yes	8 years	Dead
Bronchial carcinoma (epidermoid)	Nelson bronchus	No	10 years	Alive
Non-Hodgkin's lymphoma (immunoblastic)	Pelvic adenopathy	No	6 years	Dead*
Non-Hodgkin's lymphoma (high grade)	Digestive (stomach)	No	9 years	Dead
Osteosarcoma	Clavicle	Yes	5 years	Dead
Acute myeloblastic leukemia	—	—	6 years	Dead
Acute myoloblastic leukemia	—	—	9 years	Dead

*Death by hemorrhage due to auto-immune thrombopenia.

with the cooperative study in which our Institute took part. From 1976 to 1981, 335 patients with clinical stages I–IIIA were treated with MOPP (three to six courses according to prognostic factors) combined with radiotherapy. Patients were randomized into two groups; extended field radiotherapy (similar to our study) and irradiation restricted to the involved areas. DFS at 6 years was 88% for all patients (90% for the first group vs. 86% for the second, difference not significant). In our study, DFS is 87% at 6 years and 84% at 10 and 15 years, because there were two late recurrences at 90 and 94 months. These results are apparently comparable with those of the cooperative study; this is of great interest because the proportion of high risk HD (subgroup β plus γ) is larger in our series. However, no definitive conclusion can be drawn by comparing these two studies, since there was no randomization procedure.

Four primary failures occurred at the time of treatment. The histologic type of these chemoresistant patients was as follows: one lymphoid predominance, two nodular sclerosis and one mixed cellularity. All these four patients died of Hodgkin's disease, so CR is the best prognostic factor.

There were 11 recurrences among the 98 patients who achieved complete remission. Various controlled trials have shown that chemotherapy reduces the rate of recurrence in early stages (even in stage IIIA [31]), especially recurrence in non-irradiated areas [25], and in extra-nodal areas after subtotal or total nodal irradiation [32]. The analysis of patterns of recurrence reveals a poor prognosis for patients with contiguous extra-nodal involvement ($P = 0.008$) and/or signs of compression ($P = 0.02$). For instance, among the nine patients with a mediastinal involvement and a pulmonary contiguous extension (stage E), one early mediastinal relapse and three marginal recurrences were observed. The irradiated mediastinal field was delineated in a prone position, so with an artificial increase in mediastinal size, but also after reduction due to induction therapy. These marginal recurrences question the value of widespread irradiation delineated by the initial involvement and of irradiation with a thin lung shield, as proposed by the Stanford group [33]. Among the 15 patients with signs of compression, there was one case of mediastinal evolution despite treatment and three recurrences: one marginal recurrence which was probably due to initial pulmonary involvement (stage E), one generalized recurrence with hepatic involvement and one cervical recurrence in a patient with compressive infradiaphragmatic stage II. Rather than indicating radiotherapeutic inefficiency, these recurrences are probably due to bulky compressive tumors which were insufficiently reduced by chemotherapy. Nevertheless, even with additional induction chemotherapy, two out of 10 patients had a late recurrence at 90 and 94 months. The additional chemotherapy probably explains that the size of tumoral mass has no prognostic significance ($P = 0.08$) in this study. On the other hand, two of the four patients, with CR, but who could not receive a consolidation course because of persistent leukopenia, had an early recurrence at 3 and 17 months. This argues for the therapeutic value of the consolidation course and justifies its application, especially in patients with a high-risk HD. Indeed, there was no recurrence in patients

with a low-risk (group α, Fig. 2). However only a randomized study would be able to indicate need for a consolidation course in this group. Today it is now known that some patients with a very low-risk HD require only radiotherapy.

Nine secondary cancers occurred during follow-up. The degree to which the treatment may be incriminated is difficult to assess especially for laryngeal and bronchial carcinomas, when no information on risk factors such as nicotinism are available. However, some non-Hodgkin's lymphomas have been reported elsewhere [34] and acute leukemia and clavicle osteosarcoma in the irradiated area are certainly due to the treatment. It should be noted that one case of acute leukemia occurred 9 years after initial treatment by CVPP (two courses) and 6 years after treatment of a recurrence by MOPP (three courses). It is now known that the potential risk with MOPP is 1–2% at 10 years [35].

In summary, patients with localized stages HD can be cured with intensive but brief treatment, without surgical staging, removal or irradiation of the spleen and without maintenance therapy. The long-term results seem comparable to those with the MOPP regimen.

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