Long Term Results after 3 Courses of ABVD Plus Subtotal Nodal Radiotherapy in 188 Adult Patients with Stage I,II and IIIA Hodgin Lymphoma

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Abstract: In patients with Hodgkin lymphoma (HL) a continued improvement in outcome with a high cure rate is observed but with an increased treatment-induced late effects. We report the long-term results from 188 (stage I to IIIA) patients treated during the period 1985–94 with 3 courses of ABVD-like chemotherapy and subtotal nodal radiotherapy. 10 year overall survival is of 88% and no secondary leukaemia was observed. The main long term toxicity was cardiac, mainly related to a mediastinal dose of 45 Grays in patients with partial remission. New strategies are aiming to reduce the mediastinal dose at 30 Grays after chemotherapy-induced complete remission.

Keywords: chemotherapy, Hodgkin lymphoma, radiotherapy, ABVD

Over the past 30 years many success has been achieved in the treatment of Hodgkin lymphoma (HL) with a cure rate ranging from 80 to 90% according to initial prognostic factors and sensitivity to treatment [1]. Conversely with a long-term follow-up, patients retains an excess risk of death from other causes than HL mainly second cancers and cardiac diseases [2]. Among second cancers, acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS) were the most frequently associated with chemotherapy [3, 4, 5]. Risk of secondary leukemia was mainly correlated to MOPP chemotherapy, but large fields irradiation was also incriminated. With the aim to reduce long-term toxicity related to MOPP chemotherapy (e.g. infertility and secondary leukemia), doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) was introduced in 1975 and first results published in 1977 [6]. For these reasons, we decided in 1985 to prospectively treat early stages HL with a short course of ABVD-like chemotherapy (3 cycles to avoid cardiac toxicity related to cumulative dose of doxorubicine) followed by extended field radiotherapy (subtotal nodal irradiation at 36–40 Grays). The aim of this study was to evaluate short course of ABVD chemotherapy in this setting when the best results at this time were achieved with 6 courses of MOPP and mantle irradiation [7]. Even if extended field irradiation is not a standard nowadays, we thought interesting to review the 10-years results of this approach and to evaluate the risk of late toxicity after this combined modality.

Patients and Methods

Inclusion criteria

Patients with biopsy-proven HL presenting with a stage I to IIIA according to the Ann Arbor classification [7] were included in this prospective single-center study from June 1985 to January 1994. All patients treated in our center were included but at the date of the protocol no written inform consent was obtained. Patients with very favourable disease [e.g. stage IA, nodular sclerosis (not mediastinal) and ESR rate $<$ 50 mm] were excluded (n = 18) and treated by mantle radiation therapy (RT), this was related to their good prognosis when treated by RT alone in Stanford studies [8]. Staging procedure consisted in physical examination, chest X-ray, thoracic and abdominal CT-scan, complete blood counts, creatinine, liver function tests, ESR, LDH and bone marrow biopsy. Lymphangiography was performed

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in 85% of patients [9]. EORTC criteria (age > 50 years, > 3 nodal involved areas, mediastinal thoracic ratio > 0.35, ESR > 50 mm or ESR > 30 mm and B symptoms) were also retrospectively applied to distinguish between favourable and unfavourable patients [10]. Patients with stage IIIB and IV were treated with another protocol including 6 courses of chemotherapy with different sequences (alternating ABVD with etoposide ifosfamide regimen), secondary laparotomy and extended field RT according to surgical results [11].

Treatment

Patients received an ABVD-like chemotherapy with adriamycin 25 mg/m^2, Bleomycin 10 mg/m^2, vindesine 2 mg/m^2, dacarbazine 250 mg/m^2 on days 1 and 8 of each 28-day course for three courses. At the completion of the third cycle, all patients underwent a new staging. In case of complete or partial response, radiation therapy was initiated one month after the last dose of chemotherapy.

Radiation treatment (RT) consisted of a sequential mantle and periaortic/spleen field, according to the Standford technique [8]. All RT was delivered through anterior and posterior fields with a 18-MEV photon accelerator. The radiation doses were at 36/40 Gray in the mantle field area (with the option of a boost of 5 Gy to the involved area or residual mass), 36 Gray to the lombo-aortic field and 40 Gray to the spleen. Patients with subdiaphragmatic HL (n = 9) have all received mantle field RT after subdiaphragmatic RT.18 patients with positive lymphography on iliac lymph-nodes received total nodal irradiation at 36 Gy. Before November 89, 64% of the patients received a dose per fraction >2.2 Gray and 36% received a dose per fraction ≤2.2 Gray. After November 89, to limit pulmonary toxicity all the patients received a dose per fraction ≤2 Gray. The intervals between CT and RT and between supra and subdiaphragmatic irradiations were 4 to 6 weeks.

Response assessments and follow-up

After the end of chemotherapy, patients were categorized as having a complete response if all measurable disease had disappeared, partial response if the tumour shrinkage was superior to 75% or 50% of the initial disease, or refractory disease if there was no change or progressive disease. After treatment, patients were assessed on a bi-annual and after 5 years annual basis when possible to determine remission status and the presence of any residual toxicity. A prospective study of cardiac toxicity during the first five years have been made and published, when possible an evaluation at 10 years was planned [12]

Statistical analysis

Stopping date of analysis was 1st June 2003 and all patients were followed a minimum of 5 years after inclusion and the median follow-up is at 140 months. We focused on overall survival and analysis of cause of death. Survival was calculated according to the Kaplan-Meier method [13], from the date of first treatment to date of last follow-up or death.

Results

Patients

188 patients were included in this prospective study. Their characteristics have been previously published [14] and were summarized in Table 1.

Table 1. Characteristics of the 188 patients.

	No.	%
Age, years		
- Median	32	
- Range	15–70	
Sex		
- Male	102	54
- Female	86	46
Histology :		
- Lymphocyte predominant	10	6
- Nodular sclerosis	140	74
- Mixed cellularity	30	16
- Unclassifiable classic HL	8	4
Stage		
- I/II A	100	53
- IB/IIB	52	27
- Infradiaphragmatic I/II	9	5
- IIIA	27	15
EORTC groups*		
- Favorable	109	58
- Unfavorable	79	42
Bulky mediastinal involvement	40	21
Biological prognostic factors		
- Elevated LDH	37	22
- Anemia (Hb < 12 g/dl)	35	19
- ESR > 50 mm	65	34

Abbreviation: *reference 10; LDH : lactate dehydrogenase, ESR: erythrocyte sedimentation rate.

At the time of the study, the nodular predominance lymphocytes Hodgkin lymphoma (NPLHL) [15] was not so much separated from classical HL. And we have 10 patients in our study with lymphocyte predominant HL at pathological review. Acute toxicity was also previously described; no treatment related-deaths were observed during the treatment.

Response to Chemotherapy and Radiotherapy

At the end of chemotherapy, 90% of the patients were in complete response or partial response >75%, 9% were in partial response >50% and only two refractory patients did not receive the irradiation. Radiation consisted of subtotal nodal irradiation in 157 patients, total nodal irradiation in 17, mantle field alone in 11 with Waldeyer ring in 3 patients.

Outcome

At the end of the treatment, three patients (1.6%) were not in complete remission (primary refractory disease) and subsequently died from their disease. Median follow-up for living patients is of 140 months (60 to 200 months). After achieving complete remission, 15 patients relapsed (8%) from 5 to 96 months (median time to relapse: 18 months) and received second-line treatment with high-dose therapy and autologous stem-cell transplantation in 10. Fifty percent of relapsing patients remained alive and disease free after the second line therapy. Fertility was not prospectively studied, but no infertility has been observed and many children aroused in this young population. No pulmonary fibrosis was observed but due to the small number of ABVD courses we did not prospectively studied pulmonary functions. Hypothyroidism was found in 30% of patients needing supplementation in 20%.

The overall survival at 10 years is of 88% (Fig. 1)

The main cause of death remains HL (n = 13); 9 patients died of other causes: secondary cancers (n = 3), unknown sudden death (n = 2), cardiac disease (n = 2), and pleuropericarditis related to irradiation (n = 2) as shown on Table 1. No secondary leukemia was observed but an increasing number of solid tumors (Table 2).

Cardiac toxicity

We further analyse the 4 deaths related to cardiac toxicity which occurred in patients without any previous history of cardiac disease:

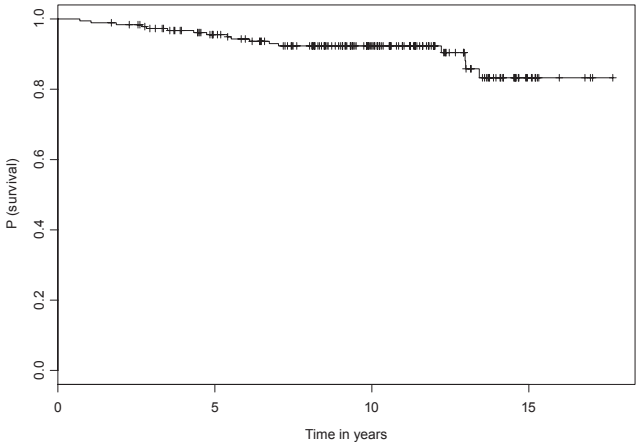

Figure 1. 0verall survival of the 188 patients with early HL.

Patient 1 female, aged 22 at diagnosis of stage IIAE (pericardium) HL in 1986 with a bulky mediastinum, and achieved a partial remission >50% after ABVD. She, than proceed to radiotherapy, mantle field at 40 Gy with a boost at 5 grays on mediastinal residual disease. One year after she developed a pleural effusion with negative histology on pleural and pericardium examination, than a pericarditis needing surgical evacuation occurred. In 1990 she developed retroperitoneal fibrosis with ascitis and recurrent pleuritis and finally died 5 years after diagnosis from malnutrition and infections related to multiple lymphatic extravasations and without relapse.

Patient 2 male aged 27 at diagnosis of stage IIA supradiaphragmatic HL and achieved partial remission with 3 courses of ABVD in 1986, mantle field was given at 45 Gy before paraaortic/spleen irradiation and he achieved a complete remission. One year after a compressive pericarditis needing surgical evacuation was diagnosed, histology of pericardium was negative. After this date, the patient needed regular pleural evacuation leading to weight loss and malnutrition and he died 6 years after diagnosis without relapse.

Patient 3 male with smoking habits, aged 42 years at diagnosis of stage IIB supradiaphragmatic HL in may 1985, he received 3 courses of ABVD and radiotherapy (subtotal nodal irradiation at 40 Gy), 2 year after diagnosis he had a pelvic relapse and was treated with etoposide ifosfamide combination and high-dose BEAM followed by autologous stem-cell transplantation in October 1988. Myocardial infarction occurred in 1993 needing angioplasty then a progressive congestive heart failure happened leading to death 18 years after diagnosis.

Table 2. Cause of deaths, age at diagnosis and median survival from the diagnosis in 22 patients.

Age	Median survival (months)	Cause of death
22	60	postradic pleuropericarditis
22	60	osteosarcoma
27	60	relapsing HL
27	24	refractory HL
27	60	postradic pleuro-pericarditis
28	36	relapsing HL
30	12	refractory HL
30	60	relapsing HL
32	40	relapsing HL
35	24	relapsing HL
36	168	unknown, no relapse
39	168	relapsing HL
41	94	relapsing HL
42	228	cardiac disease (after relapse)
43	144	metastatic adenocarcinoma
47	12	refractory HL
47	84	cardiac disease
48	48	relapsing HL
57	36	relapsing HL
57	168	anaplastic lung cancer
59	60	relapsing HL
68	72	unknown, no relapse

Patient 4 male aged 47 at diagnosis of stage IB supradiaphragmatic HL in March 1988, he received 3 courses of ABVD and radiotherapy (subtotal nodal irradiation at 40 Gy) and achieved complete remission. He had underlying hypertension and smoking habits. Hospitalization was required 6 years after treatment for cardiac insufficiency related to severe ischemic cardiopathy, he died suddenly before angioplasty.

We also observed 2 sudden deaths in patients aged 50 and 74 at death and possibly related to myocardial infarction.

Discussion

Our hypothesis of a good control of the disease with 3 courses of ABVD followed by subtotal nodal irradiation was right with a 10 year survival of 88%. A previous study from the EORTC in the same group of patients with 6 MOPP and mantle irradiation gave a 6 year survival of 89% superior to total nodal irradiation alone [7]. ABVD chemotherapy is currently considered as the gold standard for HL treatment almost in early stages, whereas in advanced stages some teams recommended higher doses regimen like BEACOPP [16]. The benefit of adding chemotherapy to STNI have been demonstrated by several randomized trial and a meta-analysis [17]. Most of these studies used chemotherapy with MOPP or COPP/ABVD, combinations which may be associated with severe toxicities (e.g. infertility and second neoplasms) and the use of ABVD with STNI improved the disease-free survival over STNI alone [18] but no data on survival were avalaible with a short follow-up. In the present study, we confirmed the efficiency of 3 courses of ABVD (which was not a standard CT in 1985) with a high response rate, and after radiation therapy, a good long-term disease control. Results are close to those of a randomized study with similar patients where ABVD was superior to regimen without alkylating agents (epirubicin, bleomycin, vinblastine and methotrexate, EBVM) [19]. EBVP (epirubicin, bleomycin, vinblastine and prednisone) in unfavourable patients is also significantly inferior to MOPP/ABV in a large randomized study from the EORTC (H7 study) [20]. We did not observe any cases of secondary leukemias which usually occurred before 10 years after initiation of treatment. It has already been noted that ABVD chemotherapy was unlikely to be associated with secondary leukemia in a large study of 761 patients with a risk of 0.6% [21]. With a follow-up of more than 10 years, the number of deaths unrelated to HL may increase and second cancer has been observed up to 20 years after initial treatment [2, 3] and are not yet evaluable. Chemotherapy including doxorubicin associated with mediastinal irradiation may increase the late cardiac toxicity of HL survivors. In the present study the total dose of doxorubicin was low (150 mg/m^2). Two patients died of cardiac disease (1%) and lethal pleuropericarditis were observed in 2 patients in partial remission who received 45 Gray in residual mediastinal mass. This dose has not been given after 1990 with the use of gallium scan to better categorize residual mediastinal mass [22]. The risk of myocardial infarction mortality has been studied in a large british cohort of 7033 HL patients treated between 1967 and 2000 [23]. This risk was 2.5 times more than expected and was correlated to supradiaphragmatic radiotherapy, anthracyclines and vincristine. The cardiotoxicity of mediastinal irradiation is well known and has been reduced in recent years with modification of irradiation techniques and limitation of the total dose given to the heart under 30 Gray. Results of randomized studies in this setting seemed to

indicate that, after chemotherapy, limited or "involved" fields gave similar long-term disease free survival than subtotal nodal irradiation [24, 25]. In conclusion, this study showed that ABVD plus subtotal irradiation gave an excellent disease control, and low middle-term toxicity. No secondary leukemia has been observed, but cardiac deaths remained of major concern in HL and further protocols aim at reducing radiotherapy, since 1998 we only use involved fields for patients with stage I/II HL.

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