Therapy of Hodgkin's lymphoma in clinical practice: A retrospective long-term follow-up analysis

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Received September 14, 2010; Accepted December 1, 2010

DOI: 10.3892/ol.2011.255

Abstract. Treatment of Hodgkin's lymphoma (HL) is perceived to be relatively straightforward. Consequently, patients are not usually referred to hemato-oncologically specialized centres and are treated locally instead. Comprehensive findings beyond prospective controlled trials are therefore lacking. Clinical data of 209 patients who had received a HL diagnosis were collected. A total of 7 patients received radiotherapy (RT) alone (3%), 75 (35%) were treated with a combination of chemotherapy (CT) and RT and 127 patients received CT alone [mainly doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD)]. Complete response (CR) following first-line treatment was achieved in 178 patients (85%) and in 195 (93%) after salvage treatment. Favorable disease (p=0.000359), limited-stage disease (p=0.0003), involvement of lymph nodes above the diaphragm (p=0.05) and absence of mediastinal bulky tumor involvement positively affected the CR rate following first-line treatment. Out of the 195 patients that achieved CR, 31 relapsed. Male gender (p=0.043) and age over 45 years (p=0.047) were significantly associated with an increased incidence of relapse. Age at diagnosis was the key factor affecting long-term outcome. The event-free survival (EFS) projected at 120 months was 80 and 57% for patients younger and older than 45 years, respectively (p=0.022). The overall survival (OS) projected at 120 months was 92 and 38% for patients younger and older than 45 years, respectively (p=0.00561). A second neoplasia was diagnosed in 8 patients. The development of a tumor in 4 cases (breast, lung and thyroid cancer) was likely RT-related. Only 1 patient not receiving RT developed acute myeloid leukemia. The EFS and OS of the 141 early-stage patients treated with CT + RT (n=62) or with CT alone (n=79) were not statistically different.

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Key words: Hodgkin's lymphoma, doxorubicin, bleomycin, vinblastine and dacarbazine, relapse, high-dose therapy

Introduction

The successful treatment of Hodgkin's lymphoma (HL) is regarded as one of the most significant accomplishments in cancer therapy over the last century. The introduction of extended field radiotherapy and mechlorethamine, vincristine, procarbazine and prednisone (MOPP) combination chemotherapy has resulted in a cure for more than 60% of patients (1). Further progress in prognostic definition has been made over the last decade (2) and a number of randomized trials compared innovative treatments to a doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD)-based approach (3-6) in order to increase the number of cured patients and to reduce short- and long-term secondary toxic effects. The standard treatment for patients with advanced-stage HL involves 6-8 courses of ABVD.

The optimal treatment strategy for early-stage HL remains a subject of intense debate (1,7). During the period between 1950 and 1980, radiotherapy (RT) was preferentially employed, since it was considered to be a less toxic curative approach as compared to MOPP. Later trials revealed that the risk of relapse in non-irradiated sites was approximately 20-30% and that a number of these relapsed patients were rescued by chemotherapy (CT). This warranted investigation to determine whether combined modality therapy (CT + RT) improves the results as compared to RT alone (8-12). A number of trials have assessed the possibility of treating HL patients with CT alone (13-15). Mounting evidence suggests that early-stage HL patients are likely to be cured by 4-6 courses of ABVD alone, thus avoiding RT altogether (1,7,16,17).

In the last 10 years, the issues addressed by large controlled trials regard mainly the role of high-dose CT with autologous

Table I. Patient clinical and histological characteristics.

Patients (n=209)	No.
Males/females (%)	99/110 (47/53)
Median age (range)	33 (14-80)
Histology	
Lymphocyte prevalence (%)	14 (7)
Classical Hodgkin's lymphoma (%)	195 (93)
Nodular sclerosis (%)	167 (80)
Lymphocyte depletion (%)	4 (2)
Mixed cellularity (%)	24 (11)
Stage	
IA (%)	16 (6)
IB (%)	2 (2)
IIA (%)	78 (37)
IIB (%)	52 (25)
IIIA (%)	11 (5)
IIIB (%)	25 (12)
IVA (%)	5 (3)
IVB (%)	20 (10)
Only lymph nodal involvement (%)	184/209 (88)
Above the diaphragm (%)	137/184 (75)
Below the diaphragm (%)	9/184 (5)
Above and below the diaphragm (%)	38/184 (20)
Bulky disease (%)	38/209 (18)
Mediastinal bulky (%)	30/209 (15)
Abdominal bulky (%)	6/209 (3)
Mediastinal involvement (%)	112/209 (53)
Hematochemical parameters	
Median leukocytes/mmc (range)	9,800 (4,000-35,000)
Median Hb gr/dl (range)	12.8 (7-17)
Median PLT/mmc (range)	400,000 (86,000-684,000)
Albumin gr/dl (range)	4 (2.3-5.2)
LDH U/l (range)	414 (132/1,900)
Median ESR (range)	40 (2-130)
Median PCR (range)	14 (1-142)
Median β2 microglobulin mg/l (range)	2 (0.5-25)

Table II. First-line treatment and response.

	No. (%)
Patients treated with RT only	7 (3)
Patients treated with CT + RT	75 (36)
Regimen combined with RT	
ABVD	39
Stanford V	25
MOPP-ABVD	4
Other	7
Patients treated with CT only	127 (61)
ABVD	114
MOPP-ABVD	7
Other	6
Response to first-line treatment	
CR	178 (85)
PR	28 (13)
NR	3 (2)
Response after salvage therapy[a]	
CR	195 (93)
PR	8 (4)
NR	6 (3)

[a]Salvage therapy was administered to 24 patients. Radiotherapy (RT), 3 patients; chemotherapy (CT) + high-dose therapy with autologous stem-cell rescue, 14 patients and CT + RT, 5 patients. CR, complete response; PR, partial response; NR, no response; ABVD, doxorubicin, bleomycin, vinblastine and dacarbazine; MOPP, mechlorethamine, vincristine, procarbazine and prednisone.

stem-cell transplant (18), new CT regimens for relapsing patients (19-21) and the reduction of RT in early stages to avoid long-term secondary effects (8,22).

However, since treatment of HL is regarded as relatively straightforward, patients are not usually referred to hemato-oncologically specialized centres and are treated locally instead. Therefore, comprehensive findings beyond prospective controlled trials are lacking. Clinical data of patients who received a diagnosis of HL in a northern Italian region (Liguria) from 1995 to 2010 were collected. These data were used to evaluate the application of novel therapeutic concepts and to verify the outcome of HL patients in comparison to what is reported by the specialized literature.

Patients and methods

The clinical data were retrospectively collected through an analysis of the records of HL patients diagnosed and treated in nine centres, including six peripheral non-specialized hospitals, from 1995 to 2010. The physicians in charge in various hospitals were interviewed to review the charts. The staging procedures included a physical examination, a total body CT scan, a bone marrow biopsy and positron emission tomography (PET).

Only patients with available follow-up information on the response to therapy, long-term outcome and toxicity were included in the study. Histological type was reassessed according to the current World Health Organization Classification (23). Bulky disease was defined as a nodal tumor mass of >10 cm for advanced stages. Patients with stage I-II, without symptoms and bulky disease, were regarded as having favorable disease. Response to therapy was previously assessed by physical and radiological imaging (ultrasonography and CT), since the use of FDG PET in defining early and final response is a recent development.

The median follow-up was 89 months (range 12-232). Overall survival (OS) was calculated from the time treatment commenced to June 30th, 2010, or at such time as patients succumbed to any cause. Event-free survival (EFS) was calculated from the date of response evaluation to June 30th, 2010, or the first event.

Table III. Factors affecting the complete response rate.

	No.	CR after first-line therapy		CR after salvage therapy	
		n (%)	p-value	n (%)	p-value
Stage			0.0500		0.1587
I	18	18 (100)		18 (100)	
II	130	113 (86)		122 (93)	
III	36	29 (80)		33 (91)	
IV	25	18 (72)		21 (84)	
Favorable Hodgkin's lymphoma	88	84 (95)	0.000359	85 (97)	0.0700
Unfavorable Hodgkin's lymphoma	121	94 (77)		109 (89)	
Early stage (I-IIA)	96	91 (94)	0.0003	93 (96)	0.0360
Advanced stage (II-B-IVB)	113	87 (77)		101 (89)	
Axillary nodes involvement	29	27 (93)	0.1900	28 (96)	0.4000
No axillary nodes involvement	180	151 (83)		166 (92)	
Exclusive lymph nodal involvement					
Above the diaphragm	137	124 (90)	0.0500	131 (95)	0.2900
Below the diaphragm	9	7 (77)		8 (88)	
Below and above the diaphragm	38	29 (76)		34 (89)	
Mediastinal involvement	110	91 (82)	0.2900	100 (90)	0.2500
No mediastinal involvement	99	87 (87)		94 (94)	
Patients with mediastinal bulky involvement	30	21 (70)	0.0300	26 (87)	0.3400
Patients with non-bulky mediastinal involvement	80	70 (87)		74 (92)	
Stage IV with marrow infiltration	11	11 (100)	0.0120	11 (100)	0.0500
Stage IV without marrow infiltration	14	8 (57)		10 (71)	
Gender			0.1500		0.5500
Male	99	88 (88)		93 (93)	
Female	110	90 (81)		101 (91)	
Age			0.8100		0.3500
≤45 years	151	127 (84)		139 (92)	
>45 years	58	48 (82)		51 (87)	

CR, complete response.

Absence of complete remission following first-line and salvage therapy, relapse and patients succumbing to any cause were considered events. Overall EFS and OS curves were calculated according to the Kaplan-Meier method. Univariate comparisons between patients in complete response (CR) vs. non-CR were performed using the Chi-square analysis or the Fisher's exact test. The impact of the variables studied was assessed by multivariate analysis according to the Cox regression model for OS and EFS, while the logistic regression model was used to evaluate the CR rate. A two-tailed p-value of ≤0.05 was considered to be statistically significant.

Patient characteristics and treatment. Table I shows the key clinical, laboratory and histological characteristics of the whole cohort of 209 adult patients. Briefly, median age was 33 years (range 14-80), with 151 patients <45 years of age. The majority of patients (80%) had classical nodular sclerosis. A total of 96 patients (45%) had limited-stage disease (I-IIA) and the remaining 113 had advanced HL. A total of 88 patients (42%) had favorable disease (stage I-IIA without bulky disease).

RT alone was administered to 7 patients (3%), 75 (35%) were treated with a combination of CT and RT, and 127 patients received CT alone. ABVD was the regimen of choice in the CT group (95%). A median of six courses was given. In the CT + RT group, 53% of the patients received ABVD and 42% the Stanford V regimen. Table II shows more detailed data on the treatment administered. RT was initiated within 1 month of the completion of CT. The target volumes for involved-field RT initially included involved nodal regions, while those for extended-field RT included the mantle field, spleen and para-aortic nodes. Patients received a median of 30 Gy.

Results

Response to therapy. The detailed responses to therapy are reported in Table II. CR after first-line treatment was achieved

Table IV. Relapse and subsequent treatment.

Relapses (%)	31/194 (16)
CR length in relapsed patients (range in months)	24 (3-130)
Therapy of relapse (%)	
CT + RT	4 (14)
CT	15 (48)
CT+ HDT	9 (29)
RT alone	3 (9)
Response to therapy at relapse (%)	
CR	23/31 (74)
PR	3/31 (9)
NR	4/31 (13)
Not evaluated	1/31 (4)
Alive without disease	22/31 (71)

CT, chemotherapy; RT, radiotherapy; HDT, high-dose therapy; CR, complete response; PR, partial response; NR, no response.

in 178 patients (85%). The early application of salvage treatment [CT ± high-dose therapy (HDT) or RT] in 31 patients who failed to obtain CR increased the number of CRs to 195 (93%).

Table III shows that a number of clinical factors affect the CR rate. Statistical analysis revealed that favorable disease (p=0.000359), limited-stage disease (p=0.0003), sub-diaphragmatic lymph node involvement (p=0.05) and absence of mediastinal bulky tumor involvement positively affected the CR rate after first-line therapy. Following the application of salvage treatment, limited stage maintained a positive effect on the CR rate (p=0.036).

Patient relapse, long-term outcome and late toxicity. Out of the 194 patients who achieved CR following first-line ± salvage treatment, 31 relapsed. Among the relapsed patients, the first CR lasted a median of 24 months (range 3-130). Treatments at first relapse are shown in Table IV. Briefly, 23 patients (74%) obtained a second CR and 22 of them remain alive and disease-free thus far.

Table V shows that male gender (p=0.043) and age >45 years (p=0.047) were significantly associated with an increased incidence of relapse. Neither advanced stage (or

Table V. Factors affecting the relapse rate.

	Patients	Relapses (%)	p-value
Stage			
I	18	5 (27)	0.185
II	122	15 (12)	
III	33	8 (24)	
IV	21	3 (14)	
Favorable Hodgkin's lymphoma	85	12 (14)	
Unfavorable Hodgkin's lymphoma	109	19 (17)	
Early stage disease (I-IIA)	93	13 (14)	0.460
Advanced stage disease (IIB-IVB)	101	18 (17)	
Axillary node involvement	28	7 (25)	0.160
No axillary node involvement	145	21 (14)	
Exclusive lymph nodal involvement			
Above the diaphragm	131	18 (13)	0.190
Below the diaphragm	8	1 (12)	
Below and above the diaphragm	34	9 (26)	
Mediastinal involvement	100	13 (13)	0.240
No mediastinal involvement	94	18 (19)	
Patients with mediastinal bulky involvement	26	3 (11)	0.740
Patients with non-bulky mediastinal involvement	74	10 (13)	
Stage IV with marrow infiltration	11	3 (27)	0.070
Stage IV without marrow infiltration	10	0 (0)	
Gender			0.043
Male	93	20 (21)	
Female	101	11 (10)	
Age			0.047
≤45 years	139	17 (12)	
>45 years	55	13 (25)	

Table VI. Long-term outcome and late toxicities.

First CR length, months (range)	70 (2-215)	
Patients alive (%)	191	(91)
Patients dead (%)	18	(9)
Overall survival, months (range)	89 (7-222)	
Median follow-up (range)	89 (7-222)	
Patients with second neoplasia (%)	8	(4)
Rectum	1	
Lung	1	
Breast	2	
Thyroid	1	
AML	2	
Endometrial carcinoma	1	
Coronary heart disease	1	
Causes of death		
Hodgkin's lymphoma	16	
Second neoplasia	1	
Acute myocardial infarction	1	

CR, complete response. AML, acute myeloid leukemia.

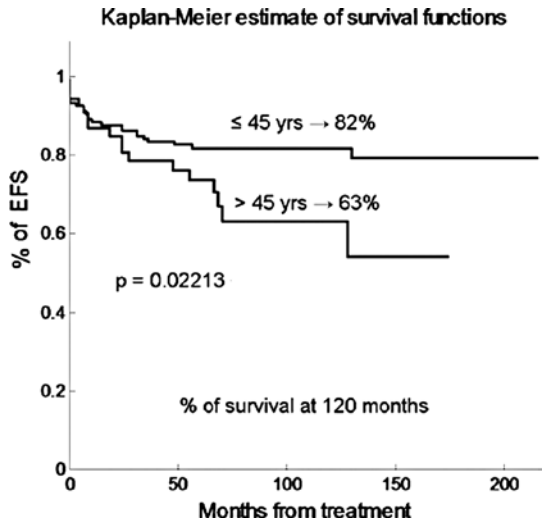

Figure 1. Age-related event-free survival (EFS) of patients with Hodgkin's lymphoma according.

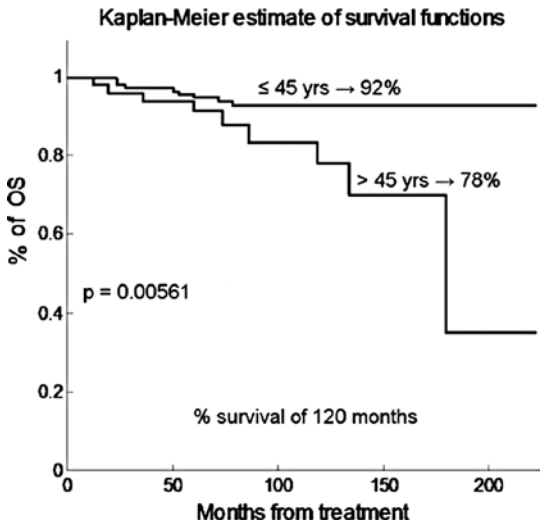

Figure 2. Age-related overall survival (OS) of patients with Hodgkin's lymphoma.

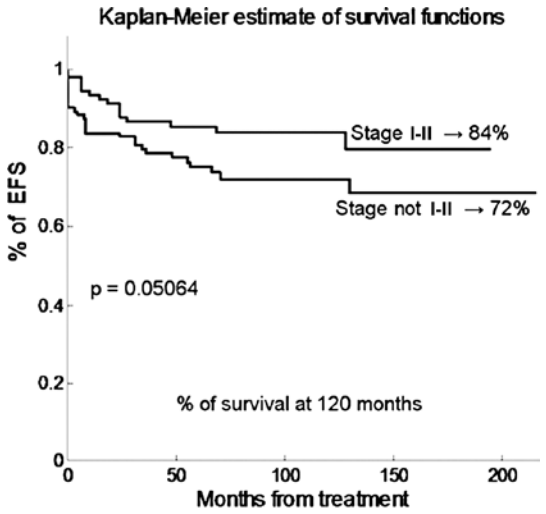

Figure 3. Stage-related event-free survival of patients with Hodgkin's lymphoma.

unfavorable disease) nor mediastinal bulky tumor involvement negatively affected the relapse rate.

A total of 191 patients (91%) remained alive after a median follow-up of 89 months. Table VI shows cause of death, which was mostly disease-related. A second neoplasia was diagnosed in 8 patients. The development of a tumor in four cases (breast, lung and thyroid cancer) was possibly RT-related. Only 1 patient not receiving RT developed acute myeloid leukemia (AML). The 2 patients who developed AML had received MOPP-ABVD and ABVD as induction treatment. One of the patients achieved CR after RT and was treated with dexamethasone, Ara-C and cisplatin (DHAP), ifosfamide, gemcitabine, vinorelbine and prednisone (IGEV) and HDT for HL relapse, while the second patient received CR after ifosfamide, epirubicin and etoposide (IEV) and HDT.

Only 1 patient treated with CT + RT developed coronary heart disease and succumbed to acute myocardial infarction.

An analysis of the clinical factors affecting EFS and OS showed that age at diagnosis was the key factor affecting long-term outcome. As shown in Fig. 1, the EFS projected at 120 months was 80 and 57% for patients younger and older than 45 years, respectively (p=0.022). Fig. 2 shows that the OS projected at 120 months was 92 and 38% for patients younger and older than 45 years, respectively (p=0.00561). Fig. 3 shows that early stage (I and II) has a borderline statistical effect on EFS (80 compared to 66% in patients with advanced disease, p=0.05), but not on OS (p=0.26). The EFS and OS of male and female individuals, of patients with favorable and unfavorable disease, of patients with or without axillary, mediastinal, marrow involvement and bulky or non-bulky disease, were not statistically different.

The EFS and OS of 141 early-stage patients treated with CT + RT (n=62) or with CT alone (n=79) were also not statistically different.

Discussion

HL is now considered to be a highly curable disease and patients are frequently diagnosed and treated in medical divisions or in peripheral oncological and hematological centres. Only primary refractory younger patients or patients showing an early relapse following the completion of treatment are referred to more specialized hematologic centres. Furthermore, the majority of patients are not enrolled in prospective clinical trials and receive therapy according to well-established clinical guidelines (24). The aim of this retrospective study was to review the current management of HL in a northern Italian region (Liguria), with special emphasis on long-term outcome and toxicity. This study confirms the previously reported clinical factors and histological distribution of HL, including the young median age of patients at diagnosis, the frequency of nodular sclerosis subtype of classical HL and the rarity of sub-diaphragmatic presentation (1). The only notable inconsistency in the reported data is that in our series female individuals were more frequently affected than males ones.

The front-line therapeutic approach almost always included CT, with only 7 patients with limited-stage disease being treated with RT alone. In stage I-II disease, first-line treatment included involved- or extended-field RT in 46% of patients.

ABVD was the regimen most frequently utilized in patients with advanced stage HL, with less than 10% of patients receiving alternative regimens. Our study shows that CT ± RT induced CR in the majority of patients (85%) and that early salvage therapy (frequently including HDT) induced CR in more than half of the patients failing to achieve CR with the first-line therapy. As previously reported (2-5), we confirm that early-stage HL and an absence of bulky tumors are statistically associated with an increased CR rate following first-line therapy. In our study, patient characteristics such as gender, age at diagnosis and mediastinal involvement did not affect the response rate. Patients with early stage HL showed a more favorable EFS than those with advanced stage disease, but only with borderline statistical significance. This observation may be related to the fact that 7 patients with early-stage disease received RT only as first-line treatment and 3 out of the 7 patients relapsed.

Long-term follow-up analysis showed a relapse rate of 16%, with 1 patient relapsing after more than 12 years. The relapse rate was lower than that reported by most recent trials (4-7,25). Male gender was associated with an increased relapse rate, but only age over 45 years was associated with an increased relapse rate and a worse EFS and OS. Among relapsed patients, we observed a favorable response to therapy, with 74% of patients achieving a second CR and more than 70% currently remaining alive and disease-free.

Overall, 23 patients (11%) with refractory or relapsed disease underwent HDT with IEV or IGEV mobilized peripheral stem cells. The low toxicity and high therapeutic efficacy of HDT contributed to the favorable outcome of our series of patients and reduced the negative prognostic relevance of advanced disease. The reduced feasibility of salvage therapy and, in particular that of HDT, in elderly patients may aid in elucidating the worse outcome of patients over 45 years of age. On the other hand, a reduced dose intensity of CT in elderly patients, mainly related to co-morbidity and toxicity, may also explain a worse EFS (26,27).

Using PET, an evaluation of early response was routinely performed in the majority of patients only in the last 2 years. However, the findings did not result in either a modification of therapy nor an earlier application of HDT. Only future randomized trials are likely to clarify the significance of early response assessment and design response-oriented strategies (28).

Long-term outcome data show that a high cure rate can be achieved with limited side effects in the vast majority of early-stage HL patients using RT + CT or CT alone, as recently reported by our group (29) and confirmed by a number of recent randomized trials (13-15).

Nonetheless, RT, especially when administered in the extended field, is associated with an increased risk of second neoplasia (22,30,31). In our series, a second tumor was diagnosed in 7 patients, following exposure to RT, although a clear relationship with RT was only found in 3 out of the 7 cases. Only one secondary AML among patients not exposed to RT was noted. In this case, the patient was treated with various lines of CT and HDT. Only 1 patient who received mediastinal RT developed coronary disease. However, an increased incidence of delayed heart complications is anticipated in the future in patients submitted to mediastinal RT, as previously reported (30,31). A longer period of observation is required to reveal small differences in toxicity and non-lymphoma-related mortality. Hoppe *et al* showed that the risk of death from Hodgkin's disease is 17% at 15 years of follow-up and increases only slightly in subsequent years, whereas the risk of succumbing to other causes is also 17% at 15 years, but increases sharply in the subsequent 25 years (22).

In conclusion, our study indicates that in our region HL is a well-known and correctly treated disease. Moreover, an efficient network between local general hospitals and specialized centres is available, allowing for the administration of treatment of a high standard throughout the entire region.

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