SPANDIDOS PUBLICATIONS

ONCOLOGY LETTERS 2: 289-295, 2011

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

SARA AQUINO[1], MARINO CLAVIO[1], EDOARDO ROSSI[1], LUANA VIGNOLO[1], MAURIZIO MIGLINO[1], MAURO SPRIANO[1], LETIZIA CANEPA[1], GIOACCHINO CATANIA[1], IVANA PIERRI[1], MICAELA BERGAMASCHI[1], ROBERTA GONELLA[1], CARLO MARANI[1], OMAR RACCHI[2], MARINA CAVALIERE[3], RICCARDO GORETTI[4], FEDERICO CARBONE[1], ANDREA BRUZZONE[1], RODOLFO TASSARA[3], ANGELO MICHELE CARELLA[1], RICCARDO GHIO[1] and MARCO GOBBI[1]

[1]Department of Haematology and Oncology, University of Genoa, St. Martino Hospital; [2]Department of Oncology, Villa Scassi Hospital, Genoa; [3]Department of Internal Medicine, St. Paolo Hospital, Savona; [4]Department of Internal Medicine, St. Corona Hospital, Pietra Ligure, Italy

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.

Correspondence to: Dr Marino Clavio, Department of Haematology and Oncology, University of Genoa, Viale Benedetto XV, N 6, 16132 Genoa, Italy
E-mail: claviom@unige.it

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.

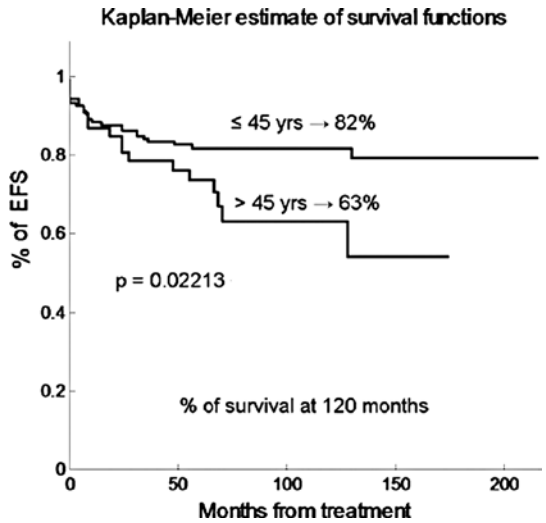

Figure 1. Age-related event-free survival (EFS) of patients with Hodgkin's lymphoma according.

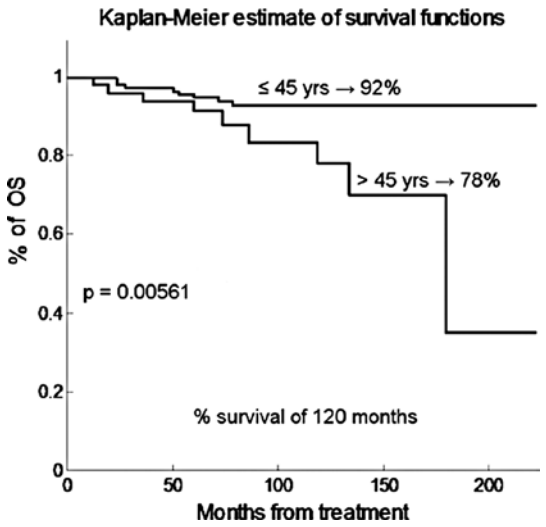

Figure 2. Age-related overall survival (OS) of patients with Hodgkin's lymphoma.

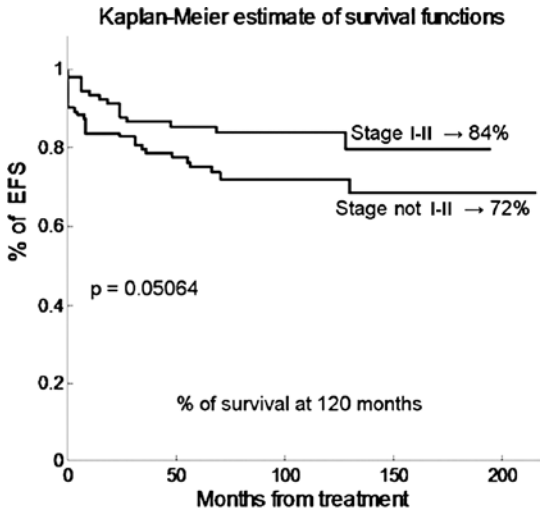

Figure 3. Stage-related event-free survival of patients with Hodgkin's lymphoma.

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.

References

1. Diehl V: Hodgkin's disease, from pathology specimen to cure. N Engl J Med 357: 1968-1971, 2007.
2. Hasenclever D and Diehl V: A prognostic score for advanced Hodgkin's disease. N Engl J Med 339: 1506-1514, 1998.
3. Canellos GP, Anderson JR, Propert KJ, *et al*: Chemotherapy of advanced Hodgkin's disease with MOPP, ABVD, or MOPP alternating with ABVD. N Engl J Med 327: 1478-1484, 1992.
4. Duggan DB, Petroni GR, Johnson JL, *et al*: Randomized comparison of ABVD and MOPP/ABV hybrid for the treatment of advanced Hodgkin's disease: report of an intergroup trial. J Clin Oncol 21: 607-614, 2003.
5. Gobbi PG, Levis A, Chisesi T, *et al*; Intergruppo Italiano Linfomi: ABVD versus modified stanford V versus MOPPEBVCAD with optional and limited radiotherapy in intermediate- and advanced-stage Hodgkin's lymphoma: final results of a multicenter randomized trial by the Intergruppo Italiano Linfomi. J Clin Oncol 23: 9198-9207, 2005.
6. Diehl V, Franklin J, Pfreundschuh M, *et al*: Standard and increased-dose BEACOPP chemotherapy compared with COPP-ABVD for advanced Hodgkin's disease. Standard and increased-dose BEACOPP. N Eng J Med 348: 2386-2395, 2003.

7. Diehl V and Fuchs M: Early, intermediate and advanced Hodgkin's lymphoma: modern treatment strategies. Ann Oncol 18 (Suppl 9): 71-79, 2007.
8. Bonadonna G, Bonfante V, Viviani S, Di Russo A, Villani F and Valagussa P: ABVD plus subtotal nodal versus involved-field radiotherapy in early-stage Hodgkin's disease: long-term results. J Clin Oncol 22: 2835-2841, 2004.
9. Koontz BF, Kirkpatrick JP, Clough RW, *et al*: Combined-modality therapy versus radiotherapy alone for treatment of early-stage Hodgkin's disease: cure balanced against complications. J Clin Oncol 24: 605-611, 2006.
10. Engert A, Franklin J, Eich HT, *et al*: Two cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine plus extended-field radiotherapy is superior to radiotherapy alone in early favorable Hodgkin's lymphoma: final results of the GHSG HD7 trial. J Clin Oncol 25: 3495-3502, 2007.
11. Fermè C, Eghbali H, Meerwaldt JH, *et al*: Chemotherapy plus involved-field radiation in early-stage Hodgkin's disease. EORTC-GELA H8 Trial. N Engl J Med 357: 1916-1927, 2007.
12. Olweny CL and Ziegler JL: Chemotherapy plus involved-field radiation in early-stage Hodgkin's disease. N Engl J Med 358: 742-759, 2008.
13. Laskar S, Gupta T, Vimal S, *et al*: Consolidation radiation after complete remission in Hodgkin's disease following six cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine chemotherapy: is there a need? J Clin Oncol 22: 62-68, 2004.
14. Straus DJ, Portlock CS, Qin J, *et al*: Results of a prospective randomized clinical trial of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) followed by radiation therapy (RT) versus ABVD alone for stages I, II, and IIIA nonbulky Hodgkin disease. Blood 104: 3483-3489, 2004.
15. Meyer RM, Gospodarowicz MK, Connors JM, *et al*: Randomized comparison of ABVD chemotherapy with a strategy that includes radiation therapy in patients with limited-stage Hodgkin's lymphoma: National Cancer Institute of Canada Clinical Trials Group and the Eastern Cooperative Oncology Group. J Clin Oncol 23: 4634-4642, 2005.
16. Gospodarowicz MK and Meyer RM: The management of patients with limited-stage classical Hodgkin lymphoma. In: ASH 2006 Educational Book, pp255-258, 2006.
17. Canellos GP, Abramson JS, Fisher DC and LaCasce AS: Treatment of favourable, limited-stage Hodgkin's lymphoma with chemotherapy without consolidation by radiation therapy. J Clin Oncol 28: 1611-1615, 2010.
18. Viviani S, Di Nicola M, Bonfante V, *et al*: Long-term results of high-dose chemotherapy with autologous bone marrow or peripheral stem cell transplant as first salvage treatment for relapsed or refractory Hodgkin lymphoma: a single institution experience. Leuk Lymphoma 51: 1251-1259, 2010.
19. Zinzani PL, Tani M, Molinari AL, Stefoni V, Zuffa E, Alinari L, Gabriele A, Bonifazi F, Salvucci M, Tura S and Baccarani M: Ifosfamide, epirubicin and etoposide regimen as salvage and mobilizing therapy for relapsed/refractory lymphoma patients. Haematologica 87: 816-821, 2002.
20. Clavio M, Garrone A, Pierri I, Michelis GL, Balocco M, Albarello A, Varaldo R, Canepa P, Miglino M, Ballerini F, Canepa L and Gobbi M: Ifosfamide, epirubicin, etoposide (IEV) and autologous peripheral blood progenitor cell transplant: a feasible and effective salvage treatment for lymphoid malignancies. Oncol Rep 14: 933-940, 2005.
21. Santoro A, Magagnoli M, Spina M, Pinotti G, Siracusano L, Michieli M, Nozza A, Sarina B, Morenghi E, Castagna L, Tirelli U and Balzarotti M: Ifosfamide, gemcitabine, and vinorelbine: a new induction regimen for refractory and relapsed Hodgkin's lymphoma. Haematologica 92: 35-41, 2007.
22. Hoppe RT: Hodgkin's disease: complications of therapy and excess mortality. Ann Oncol 8 (Suppl 1): 115-118, 1997.
23. Jaffe ES, Lee Harris N, Stein H and Vardiman JW: World Health Organization Classification of Tumors. Pathology and Genetics of Tumors of Haematopoietic and Lymphoid Tissues. IARC Press, Lyon, 2001.
24. Brusamolino E, Bacigalupo A, Barosi G, *et al*: Classical Hodgkin's lymphoma in adults: guidelines of the Italian Society of Hematology, the Italian Society of Experimental Hematology, and the Italian Group for Bone Marrow Transplantation on initial work-up, management, and follow-up. Haematologica 94: 550-565, 2009.
25. Provencio M, Salas C, Millan I, Cantos B, Sanchez A and Bellas C: Late relapses in Hodgkin Lymphoma: a clinical and immunochemistry study. Leuk Lymphoma 51: 1686-1691, 2010.
26. Walker A, Schoenfeld ER, Lowman JT, Mettlin CJ, MacMillan J and Grufferman S: Survival of the older patient compared with the younger patient with Hodgkin's disease. Influence of histologic type, staging, and treatment. Cancer 65: 1635-1640, 1990.
27. Diaz-Pavon JR, Cabanillas F, Majlis A and Hagemeister FB: Outcome of Hodgkin's disease in elderly patients. Hematol Oncol 13: 19-27, 1995.
28. Gallamini A: Positron emission tomography scanning: a new paradigm for the management of Hodgkin's lymphoma. Haematologica 95: 1046-1048, 2010.
29. Olcese F, Clavio M, Rossi E, *et al*: The addition of radiotherapy to chemotherapy does not improve outcome of early stage Hodgkin's lymphoma patients: a retrospective long-term follow-up analysis of a regional Italian experience. Ann Hematol 88: 855-861, 2009.
30. Ghalibafian M, Beaudre A and Girinsky T: Heart and coronary artery protection in patients with mediastinal Hodgkin lymphoma treated with intensity-modulated radiotherapy: dose constraints to virtual volumes or to organs at risk? Radiother Oncol 87: 82-88, 2008.
31. Travis LB: Evaluation of the risk of therapy-associated complications in survivors of Hodgkin lymphoma. Hematology Am Soc Hematol Educ Program 2007, 192-196.