Original Contribution

Response-Guided ABVD Chemotherapy plus Involved-Field Radiation Therapy for Intermediate-Stage Hodgkin Lymphoma in the Pre–Positron Emission Tomography Era: A Gruppo Italiano Studio Linfomi (GISL) Prospective Trial

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Abstract

Purpose: In the pre–positron emission tomography era, the Gruppo Italiano Studio Linfomi (GISL) investigated the feasibility and efficacy of a treatment based on a response-tailored number of doxorubicin/bleomycin/vinblastine/dacarbazine (ABVD) courses in 218 intermediate-stage Hodgkin lymphoma patients. **Patients and Methods:** Patients with stage I/II showing at least one adverse prognostic factor and stage IIIA without adverse prognostic factors were recruited. Treatment included a first step of 3 ABVD courses, followed by an early-restaging. Patients in CR/CRu received 1 additional ABVD cycle, patients in PR received 3 more ABVD, and nonresponder patients went off study. Involved-field radiation therapy (RT) was recommended on chemotherapy completion. **Results:** The median age was 30 years (range, 15-68 years) and 131 patients (61%) were female. Seven percent of patients were in stage I, 78% in stage II, and 15% in stage III; B-symptoms, bulky tumor and erythrocyte sedimentation rate > 30 were recorded in 20%, 26%, and 43% of cases, respectively. The CR/CRu rate was 62% at early restaging, 72% at the end of chemotherapy, and 95% following RT. With a median follow-up of 74 months (range, 6-193 months), 7-year overall survival, relapse-free survival, and freedom from treatment failure were 91.8% (95% CI, 86%-95.5%), 89.2% (95% CI, 82.8%-93.3%), and 81.8% (95% CI, 75.2%-86.7%), respectively. Patients in CR/CRu on early restaging, receiving 4 ABVD, had an excellent outcome with 7-year RFS and cause-specific survival similar to those of the late responders treated with 6 ABVD (RFS, 87.5% vs. 90.5% and CSS, 96.6% vs. 92.7%, respectively). **Conclusion:** The response-guided ABVD program we report, based on standard clinical staging procedures, proved to be feasible and safe in patients with intermediate-stage Hodgkin lymphoma.

Clinical Lymphoma & Myeloma, Vol. 9, No. 2, 138-144, 2009; DOI: 10.3816/CLM.2009.n.034

Keywords: Bleomycin, Dacarbazine, Doxorubicin, Early restaging, Vinblastine

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Submitted: Jul 1, 2008; Revised: Sep 29, 2008; Accepted: Oct 14, 2008

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Introduction

Treatment of Hodgkin lymphoma (HL) is commonly based on Ann Arbor Staging[1] and designed for either limited-stage disease (stage IA or IIA, bulk < 10 cm) or advanced-stage disease (B-symptoms, bulk ≥ 10 cm, or stage III-IV).[2] In Europe, patients with limited stages are split into 2 different prognostic groups, early favorable and early unfavorable (intermediate-stage), according to the presenting risk factors.[3] The main prognostic factors that qualify patients as intermediate-stage are systemic symptoms, age > 40 years or > 50 years, large mediastinal mass (> 1/3 of the maximum chest diameter), and high tumor burden (> 3 or > 4 sites of involvement, bulky mass, contiguous involvement of extranodal areas, and selected stage III cases).[4]

Though the risk factors identified from different cooperative groups differ slightly, the aforementioned definitions of intermediate stage are considered comparable.[5]

In the early 1990s, many groups started focusing on the issue of the optimal association of chemotherapy and radiation therapy (RT) to achieve the best cure rate in early-stage HL. Commonly, the extent of the therapeutic burden was planned on the basis of the tumor extension and of the prognostic factors at presentation.[6-11]

A combined-modality therapeutic approach of 4 doxorubicin/bleomycin/vinblastine/dacarbazine (ABVD) followed by involved-field (IF) RT has been demonstrated to produce the same results with less toxicity compared with 4 ABVD followed by extended-field (EF) RT,[9,10] and is currently considered the standard treatment for early-stage HL.

However, it is noticeable that intermediate-stage HL is quite a heterogeneous group, gathering patients with marked differences in terms of tumor mass. Therefore, a fixed number of chemotherapy cycles could possibly not be the best choice for such patients.

In the pre–positron emission tomography era, the Gruppo Italiano Studio Linfomi (GISL) designed a multicenter prospective trial to verify if the early achievement of a complete remission (CR) could be used as a criterion for tailoring the number of chemotherapy cycles in patients with intermediate-stage HL. The aim of the study was to explore the feasibility and efficacy of a response-guided ABVD program for intermediate-stage HL.

The number of chemotherapy courses (namely 4 or 6) was adjusted according to the tumor response evaluated on early restaging following the third ABVD cycle.

Patients and Methods

Patient Characteristics and Staging Procedures

Between January 1992 and December 2003, 218 intermediate-stage HL patients younger than 70 years of age were enrolled by 12 Italian GISL centers. As published elsewhere, intermediate stages comprised[6] the following:

(A) Stage I-II plus at least one of the following: bulky involvement (mediastinal mass > 1/3 of the maximum chest diameter at T5-T6 level, and/or peripheral or retroperitoneal adenopathy > 6 cm in its largest diameter), unfavorable histology (nodular sclerosis type II or lymphocyte depleted), or systemic symptoms

(B) Stage I_A-III_A with extranodal extension

(C) Stage III_A with histologic types other than nodular sclerosis type II or lymphocyte depleted

Histopathologic diagnosis was made by the local pathologist according to the Rye modification of Lukes and Butler classification.[12] Staging procedures and assessment of response to therapy were clinically performed according to the Cotswolds meeting criteria.[13] Besides careful physical examination, pretreatment evaluations comprised complete blood count, serum biochemistries including liver function tests, lactic acid dehydrogenase, erythrocyte sedimentation rate (ESR), chest x-rays, computed tomographic (CT) scan of both chest and abdomen, and bone marrow trephine biopsy.

Treatment Plan

The ABVD regimen was delivered according to the drugs dosages and schedule as indicated in the original report[14] and consisted of doxorubicin 25 mg/m^2, bleomycin 10 U/m^2, vinblastine 6 mg/m^2, and dacarbazine 375 mg/m^2 intravenously on days 1 and 15. Chemotherapy was recycled every 28 days. Treatment included a first block of 3 ABVD cycles followed by an early restaging, then 1 or 3 more ABVD cycles were administered to patients on CR or PR, respectively. Overall, patients who achieved a CR or CRu (early responders; ERs) received 4 ABVD cycles, whereas those who did not achieve such a result (late responders; LRs) received a complete course of 6 ABVD. Patients who experienced a response less than PR after the first ABVD block went off study and received second-line therapy according to the local policies. Involved-field RT was recommended following ABVD courses at a dose of 30 Gy on sites involved at diagnosis.

Because guidelines for the use of granulocyte colony-stimulating factors (G-CSFs) were not specified at the time of the study design, G-CSF was administered at physician's discretion to patients who experienced severe neutropenia.

Consolidative Radiation Therapy

The planned RT dose was 30 Gy to all fields starting 4-6 weeks after completion of chemotherapy. Single-fraction size was 1.8-to-2.0 Gy, given 5 times a week. Additional RT of 10 Gy was administered during the fourth week on sites of initial bulky disease. Irradiation was administered to all the sites involved at diagnosis.[15] X-rays' energy, dose prescription, and technique of irradiation (parallel opposed fields and direct field) varied according to the disease's presentation. Irradiation was administered to all the involved regions with one single field, whenever possible.

Response Criteria

Responses to therapy were categorized according to Cotswolds criteria.[13] The first restaging was performed after the third ABVD course. Restaging was then repeated one month after completion of chemotherapy (fourth or sixth cycle) and 1 month after RT.

Patients in CRu at the end of the treatment plan were considered in posttreatment CR, provided that the residual mass did not increase within 6 months of the completion of therapy. Remission status was checked every 3 months during the first year, then twice a year until the fifth year, and once a year thereafter.

Statistical Analysis

Data were analyzed as of June 2008. All the patients who entered the study were analyzed for prognostic factors, response

Table 1 Pretreatment Characteristics of the Whole Series

Characteristic	Number of Patients (%)
Total	206 (100)
Sex	
Male	85 (41)
Female	121 (59)
Age, Years	
≤ 45	163 (80)
≥ 45	43 (20)
Stage	
I	16 (7)
II	160 (78)
III	30 (15)
NS Histology	162 (79)
> 3 Involved Sites*	28 (16)
Extranodal Disease	12 (6)
Bulky Disease†	51 (26)
Bulky Mediastinum	21 (11)
ESR ≥ 30	83 (40)
B Symptoms Present	41 (20)
IPS‡	
0-1	113 (55)
2	44 (21)
≥ 3	18 (9)

*Missing value in 20 cases.
†Missing value in 29 cases.
‡Missing value in 31 cases.
Abbreviations: ESR = erythrocyte sedimentation rate; IPS = International Prognostic Score; NS = nodular sclerosis

to treatment, and survival data (freedom from treatment failure [FFTF], relapse-free survival [RFS], overall survival [OS], and cause-specific survival [CSS]). The objective of the study was to investigate the feasibility and efficacy of a flexible number of ABVD cycles, namely 4 or 6, according to the clinical response obtained at the early restaging. The comparison of the outcome of the two subgroups of patients (ER and LR) was performed by taking into account only patients who actually completed the planned chemotherapy and RT (informative patients).

Overall survival was calculated from treatment start to death from any cause or last follow-up. Cause-specific survival was calculated as OS taking into account only deaths related to the lymphoma. Relapse-free survival was calculated from the date of CR achievement to the date of relapse. Freedom from treatment failure was defined as the time elapsed from the start of chemotherapy to progression during therapy, lack of complete remission, relapse, or death from any cause. Survival estimates were calculated by means of the Kaplan-Meier product limit method[16] and compared using the log-rank test.[17] Cutoff values used to categorize continuous variables were based on values found to be significantly predictive of outcome in previously published literature.[4,18] The χ^2 test or, when appropriate, the Fisher exact test (2-tailed) was used to compare qualitative data. Factors independently associated with an early attainment of CR were identified on multivariate analysis by the Cox proportional hazard regression model.[19] The multivariate model included all the variables observed at diagnosis which proved to be associated with an early CR on univariate analysis. All confidence intervals (CIs) were reported at a level of 95%. The limit of significance for all analyses was defined as a *P* value < .05.

Table 2 Clinical Presenting Features of Early- and Late-Responding Patients

Characteristic	Early Responders, %	Late Responders, %	*P* Value
Male Sex	42	40	.771
Age ≥ 45 Years	24	16	.216
Bulky	23	29	.409
Bulky Mediastinum	13	14	.834
ESR ≥ 30	46	51	.542
B Symptoms	17	23	.368
Involved Sites ≥ 3	21	31	.1
IPS ≥ 3	11	10	.95
Ann Arbor Stage			
I	6	5	.007
II	86	69	
III	8	25	

Abbreviations: ESR = erythrocyte sedimentation rate; IPS = International Prognostic Score

Results

From January 1992 to December 2003, 218 consecutive patients were entered in this trial. A total of 12 patients were not qualified for this study and were excluded from additional analysis. Reasons for exclusion were wrong stage/risk factors (n = 2), incomplete data on staging (n = 7), and lost at follow-up after the first ABVD cycle (n = 3).

Table 1 reports the main characteristics of the whole series. The median age was 30 years (range, 15-68 years), with 20% of patients aged > 45 years and a male-to-female ratio of 0.7. Nodular sclerosis histology accounted for 75% of cases. Seven percent of patients were in stage I, 78% were in stage II, and 15% in stage III; B-symptoms, bulky tumor, and ESR > 30 were recorded in 20%, 26%, and 40% of cases, respectively. Subdiaphragmatic disease was documented in 12 cases (6%) and extranodal localizations (14 cases, 7%) included lung (6), salivary glands (2), Waldeyer's ring (2), pleura (1), breast (1), and thyroid (2).

Response to Therapy

A total of 206 patients were object of the present analysis. After the first ABVD block, 59% of patients were in CR/CRu, and 37% were in PR. Five patients who had a response less than PR, and 4 patients who were lost before early restaging were computed as failures (4%). Table 2 summarizes the presenting data of patients

subdivided according to the clinical response at early restaging. Because of physicians' decision or patients' choice, 11 early responders had a full six-cycle course of chemotherapy. Overall, 111 patients received 4 ABVD, and 86 patients received 6 ABVD.

Several prognostic factors, such as age, stage, disease bulk, mediastinal involvement, ESR, number of involved areas, International Prognostic Score (IPS) ≥ 3, male sex, and histologic subtype, were assessed for their influence on the promptness of CR achievement. Only stage III significantly correlated with a late attainment of CR.

Eighty-five per cent of patients (93% of early responders and 82% of late responders) received the planned IF-RT. Twenty-four out of 27 (88.9%) patients who were in PR at the end of chemotherapy and 22 out of 44 (50%) CRu patients obtained a CR following RT, with an overall response rate at the end of the therapeutic program of 95.5% (CR, 83%; CRu, 11%; PR, 1.5%).

Outcome

Progressive disease or relapse occurred in 26 patients (13%), 2 months to 8.6 years after the start of therapy. Fifteen deaths (7%) were recorded, 9 of them were because of HL and 6 were unrelated to HL (namely, 2 myocardial infarctions, 2 sudden deaths, 1 lung cancer, 1 anaplastic large cell lymphoma). Second malignancies were diagnosed in 8 patients (3.8%) 2.8-9 years after the treatment start.

Overall, 11 patients did not respond to treatment (6 to chemotherapy, and 5 to RT) and were given salvage therapies. Seven of them obtained a CR, and 2 out of these 7 relapsed and died of HL. Of the remaining 4 unresponsive patients, 2 died of HL and 2 were lost at follow-up. Relapses were recorded in 18 patients (9.6%), 3 occurring in previously irradiated fields, and 1 occurring in a patient who did not receive RT. All relapsed patients received salvage therapy that included high-dose chemotherapy supported by autologous stem cell transplantation (ASCT) in 11 cases. With a median follow-up of 62 months (from first CR achievement), 12 patients were in second or subsequent remission, and 5 patients died of progressive lymphoma.

With a median follow-up of 74 months (range, 6-193 months) the 7-year FFTF for the whole series was 81.8% (CI, 75.2%-86.7%), the RFS was 89.2% (CI, 82.8%-93.3%), the OS was 91.8% (CI, 86%-95.5%; Figures 1-3), and the CSS was 94.6% (CI, 89.2%-97.4%; not shown).

Outcome According to the Promptness of Response

This comparison was restricted to 170 patients (103 ER and 67 LR) who actually received the planned chemotherapy and RT program. Sixteen relapses were recorded in the 165 patients who were in CR at completion of therapy. Relapses were equally distributed among the 2 groups: 10 belonged to ER (9.3%) and 6 to LR (9%). Patients receiving ASCT as salvage therapy were equally distributed between the ER and LR groups. Overall, 10 deaths were recorded; 7 of them were lymphoma related, 5 occurring among LR and 2 among ER.

The 7-year RFS, OS, and CSS rates for the early responders were 87.5% (CI, 76.2%-93.7%), 92.3% (CI, 82.4%-97.5%), and 96.6% (CI, 86.6%-99.2%), respectively.

For the late responders, the 7-year RFS, OS, and CSS rates were 90.5% (CI, 80.1%-95.6%), 92.7% (CI, 80.1%-97.3%), and 92.7% (CI, 80%-97.3%), respectively. The differences between early and late responders did not reach statistical significance even after IPS adjustment. Outcome according to the promptness of response to therapy is plotted in Figures 4-6.

Toxicity

Acute toxicity following ABVD was moderate and, as expected, slightly more intense in the group of patients who received six ABVD cycles compared with those who received only 4 ABVD. Grade 3/4 leukopenia was observed in 38% of patients receiving 4 ABVD versus 58% of those receiving 6 ABVD ($P = .03$), anemia in 2% versus 19% ($P = .003$), and infection in 2% versus 3% (P = not significant). No grade 3/4 thrombocytopenia was recorded. Four patients developed lung fibrosis following RT, and 3 developed hypothyroidism. Two patients developed myocardial infarction, and 1 was diagnosed with a dilatative cardiomyopathy. Six patients were diagnosed with a second malignancy during the follow-up: 2 non–small-cell lung cancers, 1 chraniopharyngioma, 1 chronic myeloid leukemia, 1 germ-cell tumor of the testis, and 1 anaplastic large-cell non-Hodgkin lymphoma.

Discussion

When the current study was started in the early 1990s, the therapy for intermediate-stage HL was still largely based on EF-RT,[20-22] but awareness was growing about the occurrence of severe RT-related late toxicities.[23-25] It became evident that the incidence of RT-related deaths exceeded that of Hodgkin-related ones in long-term follow-up.[26] Therefore, many cooperative groups started exploring whether the introduction of chemotherapy and the reduction of the radiation dose could reduce toxicity without affecting the cure rate.[27-30]

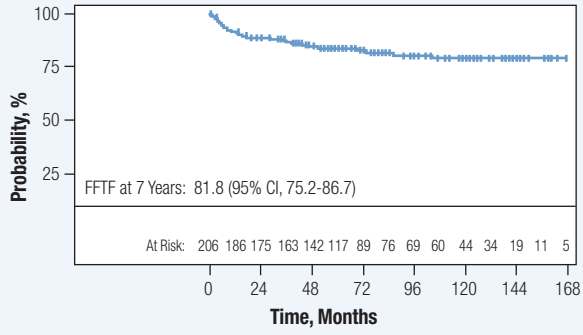
At that time, both the appropriate regimen of chemotherapy and the number of cycles for this setting of patients were unknown,[31] yet in the early 1980s, some reports suggested the favorable prognostic value of a prompt clinical response in HL treated with chemotherapy.[32-34]

The GISL wanted to explore whether the number of chemotherapy cycles could be customized on the basis of the promptness of the clinical response. At the time of the study design, the hypothesis that an early response could be linked to a good prognosis, although reasonable, was quite new.[35] Furthermore, prospective verifications were lacking and a modification of the duration of therapy based on this criterion was unprecedented.

The study implied a certain degree of complexity requiring the interpolation of a staging procedure between the third and the fourth cycle of chemotherapy. The first point to explore was the feasibility of such an approach on a multicentric, nationwide scale. Overall, the adherence to the protocol was satisfactory with only 4 patients missing the early re-staging evaluation and < 7% of cases receiving a full course of 6 ABVD albeit in early CR.

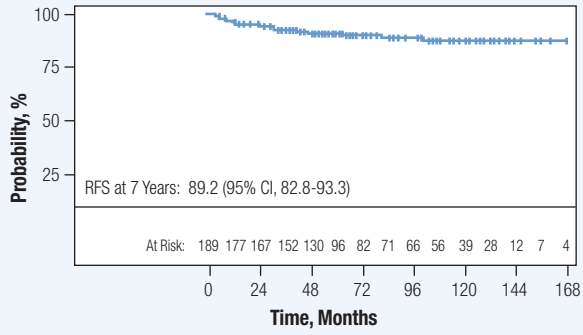
Our trial provided evidence supporting the effectiveness of a response-oriented therapeutic strategy in adult HL patients.[36,37] Shortening the duration of chemotherapy in patients who attained a CR within the third cycle proved not to affect the outcome. With a flexible program we were able to reduce by 30% the number of chemotherapy cycles (ie, from 6 to 4) in 111 (56%) intermediate-stage HL patients. The OS and FFTF of the whole series matched

Figure 1 Freedom From Treatment Failure



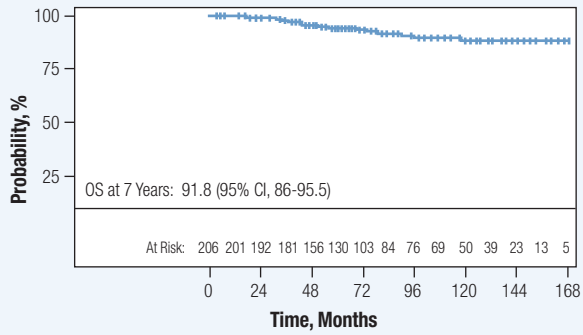
Abbreviation: FFTF = freedom from treatment failure

Figure 2 Relapse-Free Survival



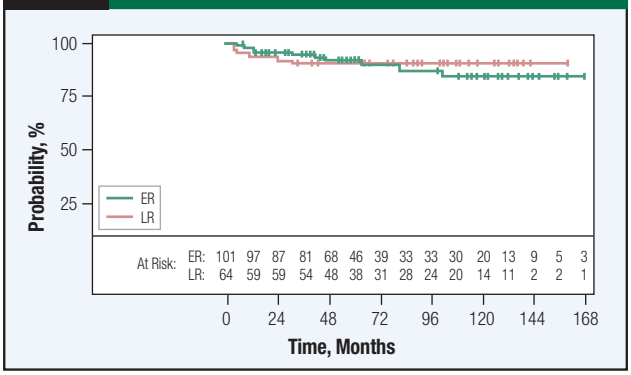
Abbreviation: RFS = relapse-free survival

Figure 3 Overall Survival



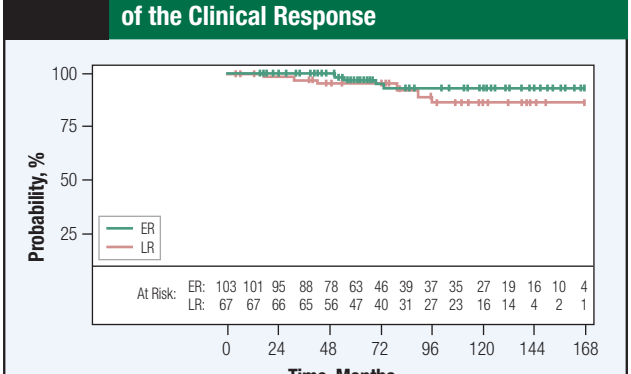
Abbreviation: OS = overall survival

Figure 4 Relapse-Free Survival According to the Promptness of the Clinical Response



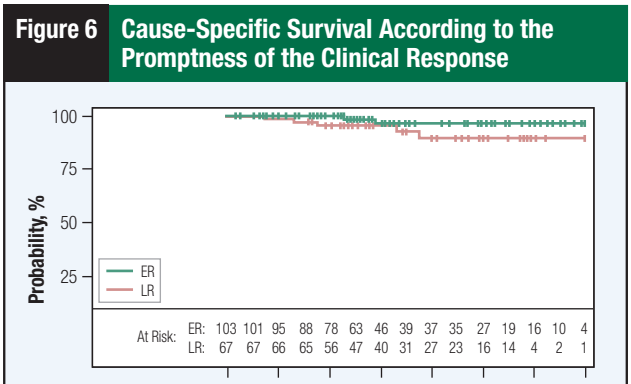
Abbreviations: ER = early responders; LR = late responders

Figure 5 Overall Survival According to the Promptness of the Clinical Response



Abbreviations: ER = early responders; LR = late responders

Figure 6 Cause-Specific Survival According to the Promptness of the Clinical Response



Abbreviations: ER = early responders; LR = late responders

favorably with those expected for this setting of patients.[3,10,11] Restricting the analysis to those patients who actually received the complete planned course of chemotherapy and IF-RT, the group of patients who received only 4 ABVD had similar outcome in terms of RFS, OS, and CSS compared with those who received 6 ABVD. However, we would like to acknowledge that, because of the CT scan–based nature of the clinical restaging performed in our trial, an accurate discrimination between signs of residual fibrosis and those of active residual disease was not possible in patients with residual imaging abnormalities on early re-staging. Therefore, we cannot rule out that some of these patients who were actually in CR after 3 ABVD cycles could have been misclassified as PR and thus received a full course of 6 ABVD.

The influence of the quality of the response to chemotherapy on the outcome has been assessed in the EORTC-GELA H8 trial, whose results have been recently published.[11] In the H8 trial, 3 different therapy regimens were compared in the unfavorable

HL arm, namely 6 cycles of MOPP-ABV plus IF-RT, 4 cycles of MOPP-ABV plus IF-RT, and 4 cycles of MOPP-ABV plus subtotal nodal RT. The CR/CRu rates did not differ among the 3 treatment groups, and the quality of response to chemotherapy (CR or PR), evaluated by standard clinical restaging, did not correlate with the risk of relapse. However, it should be noticed that in the H8 trial the clinical response was assessed upon completion of chemotherapy, namely after 4 or 6 cycles, whereas in our analysis it was evaluated after the third chemotherapy cycle (ie, 1-3 months earlier than in the H8 trial).

Recently, several studies in which no interim change of therapy was allowed, have shown that a negative PET scan after 2 chemotherapy cycles (PET-2) correlates with an excellent progression-free survival (PFS).[38-40]

A joint Duch-Italian study demonstrated a 2-year PFS of 95% for the patients with a negative PET-2 and a PFS of 12.8% for PET-2–positive patients.[41]

Dann et al have reported a prospective non randomized trial on a risk and response-adapted BEACOPP regimen. With this approach, featuring a restaging after the second cycle, including PET evaluation, they found similar EFS and OS for patients with low- and high-risk HL.[42]

However, the definition of early response based on fluorodeoxyglucose (FDG)–PET scan is not comparable to that of anatomic CR. FDG-PET is actually a "glucose scan" and not a "cancer scan,"[43] and a negative PET-2 scan indicates that chemotherapy has blunted the proliferative capacity of the tumor, not providing data regarding the size and viability of the residual tumor mass. Differently, an early CT-based CR refers to the anatomic reduction of the tumor burden under the CT resolution capability. Therefore, our results are hardly comparable to those obtained with a FDG-PET-2 restaging.

The primary aim of the current study was to avoid unnecessary chemotherapy to patients, on the basis of the promptness of their clinical response. In light of our results, a restaging after 3 chemotherapy courses based on clinical and CT evidences, seems to be adequate for fulfilling this purpose in intermediate-stage HL patients.

Conclusion

In conclusion, our data show that a reduction of the chemotherapy burden based on the promptness of the clinical response is feasible and safe in HL patients. To further improve the survival of patients who lack an early response, a shift toward more intensive treatments (eg, BEACOPP) could be explored. Some trials are currently ongoing in Europe that aim to challenge this hypothesis by means of response-guided treatment policies based on FDG-PET-2 restaging.

Disclosures

The authors report no relevant conflicts of interest.

References

1. Rosenberg SA. Report of the committee on Hodgkin's disease staging procedures. *Cancer Res* 1971; 31:1862-3.
2. Connors JM. State-of-the-art therapeutics: Hodgkin's lymphoma. *J Clin Oncol* 2005; 23:6400-8.
3. Diehl V, Thomas RK, Re D, Part II. Hodgkin's lymphoma—diagnosis and treatment. *Lancet Oncol* 2004; 5:19-26.
4. Specht L, Hasenclever D. Prognostic factors. In: Hoppe RT, Mauch PT, Armitage JO, Diehl V, Weiss LM, eds. *Hodgkin's disease*. Philadelphia: Lippincott Williams &Wilkins; 2007:152-69.
5. Gisselbrecht C, Mounier N, Andre M, et al. How to define intermediate stage in Hodgkin's lymphoma? *Eur J Haematol* 75:111–114, 2005 (suppl 66)</unknown>
6. Gobbi PG, Pieresca C, Cavanna L, et al. CCNU, vinblastine, procarbazine and prednisone (CVPP) with extended-field radiotherapy in the treatment of early unfavorable Hodgkin's disease. A prospective study on behalf of the Gruppo Italiano per lo Studio dei Linfomi (GISL). *Haematologica* 1996; 81:503-12.
7. Anselmo AP, Cavalieri E, Osti FM, et al. Intermediate stage Hodgkin's disease: preliminary results on 210 patients treated with four ABVD chemotherapy cycles plus extended versus involved field radiotherapy. *Anticancer Res* 2004; 24:4045-50.
8. Noordijk EM, Carde P, Dupouy N, et al. Combined-modality therapy for clinical stage I or II Hodgkin's lymphoma: long-term results of the European Organisation for Research and Treatment of CancerH7 randomized controlled trials. *J Clin Oncol* 2006; 24:3128-35.
9. Bonadonna G, Bonfante V, Viviani S, et al. ABVD plus subtotal nodal vs involved field radiotherapy in early stage Hodgkin's disease: long-term results. *J Clin Oncol* 2004; 22:2835-41.
10. Engert A, Schiller P, Josting A, et al. Involved-field radiotherapy is equally effective and less toxic compared with extended-field radiotherapy after four cycles of chemotherapy in patients with early-stage unfavorable Hodgkin's lymphoma: results of the HD8 trial of the German Hodgkin's Lymphoma study group. *J Clin Oncol* 2003; 21:3601-8.
11. Fermé C, Eghbali H, Meerwaldt JH, et al. EORTC-GELA H8 Trial. Chemotherapy plus involved-field radiation in early-stage Hodgkin's disease. *N Engl J Med* 2007; 357:1916-27.
12. Lukes RJ, Butler JJ. The pathology and nomenclature of Hodgkin's disease. *Cancer Res* 1966; 26:1063-83.
13. Lister TA, Crowther D, Sutcliffe SB, et al. Report of a committee convened to discuss the evaluation and staging of patients with Hodgkin's disease: Cotswolds meeting. *J Clin Oncol* 1989; 7:1630-6.
14. Bonadonna G, Zucali R, Monfardini S, et al. Combination chemotherapy of Hodgkin's disease with adriamycin, bleomycin, vinblastine, and imidazole carboxamide versus MOPP. *Cancer* 1975; 36:252-9.
15. Yahalom J, Mauch P. The involved field is back: issues in delineating the radiation field in Hodgkin's disease. *Ann Oncol* 2002; 13(suppl 1):79-83.
16. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958; 53:457-81.
17. Kalbfleisch JD, Prentice RL. The Statistical Analysis of Failure Time Data. New York, NY: Wiley; 1980.
18. Gobbi PG, Zinzani PL, Broglia C, et al. Comparison of prognostic models in patients with advanced Hodgkin's disease. *Cancer* 2001; 91:1467-78.
19. Cox DR. Regression models and life table. *J Stat Soc* 1972; 34:187-220.
20. Mauch P, Terbell D, Weinstein H, et al. Stage IA and IIA supradiaphragmatic Hodgkin's disease: prognostic factors in surgical with staged patients in surgical with staged patients treated with mantle and paraaortic irradiation. *J Clin Oncol* 1988; 6:1576-83.
21. Cimino G, Biti GP, Anselmo AP, et al. MOPP chemotherapy versus extended field radiotherapy in the management pathological stages I-IIA Hodgkin's disease. *J Clin Oncol* 1989; 7:732-7.
22. Tubiana M, Henry-Amar M, Carde P, et al. Toward comprehensive management tailored to prognostic factors of patients with clinical stages I and II in Hodgkin's disease. The EORTC Lymphoma Group Controlled Clinical Trials: 1964-1987. *Blood* 1989; 73:47-56.
23. Hancock SL, Tucker MA, Hoppe RT. Factors affecting late mortality from heart disease after treatment of Hodgkin's disease. *JAMA* 1993; 270:1949-55.
24. Henry-Amar M, Hayat M, Meerwaldt JH, et al. Causes of death after therapy for early stage Hodgkin's disease entered on EORTC protocols. EORTC Lymphoma Cooperative Group. *Int J Radiat Oncol Biol Phys* 1990; 19:1155-7.
25. Henry-Amar M. Second cancer after the treatment for Hodgkin's disease: a report from the International Database on Hodgkin's Disease. *Ann Oncol* 1992; 3(suppl 4):117-28.
26. van Leeuwen FE, Swerdlow AJ, Travis LB. Second cancers after treatment of Hodgkin lymphoma. In: Hoppe RT, Mauch PT, Armitage JO, Diehl V, Weiss LM, eds. *Hodgkin's disease*. Philadelphia: Lippincott Williams &Wilkins; 2007:339-62.
27. Sieber M, Tesch H, Pfistner B, et al. Rapidly alternating COPP/ABV/IMEP is not superior to conventional alternating COPP/ABVD in combination with extended-field radiotherapy in intermediate-stage Hodgkin's Lymphoma: final results of the German Hodgkin's Lymphoma study group trial HD5. *J Clin Oncol* 2002; 20:476-84.
28. Le Maignan C, Desablens B, Delwail V, et al. Three cycles of Adriamycin, bleomycin, vinblastine, and dacarbazine (ABVD) or epirubicin, bleomycin, vinblastine, and methotrexate (EBVM) plus extended field radiation therapy in early and intermediate Hodgkin disease: 10-year results of a randomized trial. *Blood* 2004; 103:58-66.
29. Press OW, LeBlanc M, Lichter AS, et al. Phase III randomized intergroup trial of subtotal lymphoid irradiation versus doxorubicin, vinblastine, and subtotal lymphoid irradiation for stage IA to IIA Hodgkin's disease. *J Clin Oncol* 2001; 19:4238-44.
30. 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* 2004; 104:3483-9.
31. Loeffler M, Brosteanu O, Hasenclever D, et al. Meta-analysis of chemotherapy versus combined modality treatment trials in Hodgkin's disease. International Database on Hodgkin's Disease overview study group. *J Clin Oncol* 1998; 16:818-29.
32. Levis A, Vitolo U, Ciocca Vasino MA, et al. Predictive value of early response to chemotherapy in high risk stage II and III Hodgkin's disease. *Cancer* 1997; 60:1713-9.
33. Kuentz M, Reyes F, Brun J, et al. Early response to chemotherapy as prognostic factor in Hodgkin's disease. *Cancer* 1983; 52:780-5.
34. Bjorkholm M, Axdorph U, Grimfors G, et al. Fixed versus response-adapted MOPP/ABVD chemotherapy in Hodgkin's disease. A prospective randomized trial. *Ann Oncol* 1995; 6:895-9.
35. Carde P, Koscielny S, Frankin J, et al. Early response to chemotherapy: a surrogate for final outcome of Hodgkinn's disease patients that should influence initial treatment length and intensity? *Ann Oncol* 2002; 13(suppl 1):86-91.
36. Lanman-Parker J, Pacquement H, Leblanc T, et al. Localized Childhood Hodgkin's disease: Response-adapted chemotherapy with Etoposide, Bleomicyn, Vinblastine, and Prednisone before low-dose radiation therapy. Results of the French society of Pediatric Oncology study MDH90. *J Clin Oncol* 2000; 7:1500-7
37. Hudson MH, Krain M, Link MP, et al. Risk-adapted, combined modality therapy with VAMP/COP and response-based, involved-Field radiation for unfavourable pediatric Hodgkin's disease. *J Clin Oncol* 2004; 22:4541-50.
38. Gallamini A, Rigacci L, Merli F, et al. The predictive value of positron emission tomography scanning performed after two courses of standard therapy on treatment outcome in advanced stage Hodgkin's disease. *Haematologica* 2006; 91:475-81.
39. Hutchings M, Loft A, Hansen M, et al. FDG-PET after two cycles of chemotherapy predicts treatment failure and progression-free survival in Hodgkin lymphoma. *Blood* 2006; 107:52-9.
40. Zinzani PL, Tani M, Fanti S, et al. Early positron emission tomography (PET) restaging: a predictive final response in Hodgkin's disease patients. *Ann Oncol* 2006; 17:1296-300.
41. Gallamini A, Hutchings M, Rigacci L, et al. Early interim 2-[18F]fluoro-2-deoxy-D-glucose positron emission tomography is prognostically superior to international prognostic score in advanced-stage Hodgkin's lymphoma: a report from a joint Italian-Danish study. *J Clin Oncol* 2007; 25:3746-52.
42. Dann EJ, Bar-Shalom R, Tamir A, et al. Risk-adapted BEACOPP regimen can reduce the cumulative dose of chemotherapy for standard and high-risk Hodgkin lymphoma with no impairment of outcome. *Blood* 2007; 109:905-9.
43. MacManus MP, Seymour JF, Hicks RJ. Overview of early response assessment in lymphoma with FDG-PET. *Cancer Imaging* 2007; 7:10-8.