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Stage I-IIA Non-Bulky Hodgkin Lymphoma. Is Further Distinction Based on Prognostic Factors Useful? The Stanford Experience

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Abstract

Purpose—In the US, early stage Hodgkin lymphoma (HL) is defined as asymptomatic stage I/II non-bulky (mediastinal mass ratio <1/3) disease. European groups stratify patients to more intense treatment by considering additional unfavorable factors, such as age, number of nodal sites, sedimentation rate, extranodal disease, and elements of the international prognostic score for advanced HL. We sought to determine the prognostic significance of these factors in patients with early stage disease treated at Stanford.

Patients and Methods—This was a retrospective analysis on 101 patients treated with abbreviated Stanford V chemotherapy (8 weeks) and 30 Gy (n=84) or 20 Gy (n=17) radiotherapy to involved sites. Outcomes were assessed after applying European risk factors.

Results—At a median follow-up of 8.5 years the freedom from progression (FFP) and overall survival (OS) were 94% and 97% respectively. 33-60% of our patients were unfavorable per European criteria (GHSG n=55%, EORTC n=33% and GELA n=61%). Differences in FFP between favorable and unfavorable patients were significant only for GHSG (p=0.02) with no difference in OS with any criteria. Five of 6 patients who relapsed were successfully salvaged.

Conclusions—The majority of our patients deemed unfavorable had an excellent outcome despite a significantly abbreviated regimen. Application of factors used by the GHSG defined a less favorable subset for FFP, but with no impact on OS. As therapy for early stage disease moves to further reductions in therapy, these factors take on added importance in the interpretation of current trials results and design of future studies.

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Introduction

Early stage favorable Hodgkin lymphoma (HL) is defined at most centers in the United States (US) as stage I-IIA disease in the absence of large mediastinal adenopathy (mediastinal mass ratio [MMR] $< 1/3$ of the maximum intrathoracic diameter) or bulky disease ≥ 10 cm. Other groups, such as the European Organization of Research and Treatment of Cancer (EORTC), the German Hodgkin Study Group (GHSG), and the Groupe d'Etudes des Lymphomes de l'Adulte (GELA) have further stratified patients with non-bulky stage I-II disease as favorable or unfavorable based on several additional risk factors including age, number of involved nodal sites, erythrocyte sedimentation rate (ESR), presence of extranodal (EN) disease and elements of the international prognostic score (IPS) for advanced HD.(1-4) The EORTC and GHSG have used these prognostic factors to determine assignment to specific clinical trials, for example EORTC H8F versus H8U, or GHSG HD10 versus HD11.(5)-(6) In recent trials, patients with favorable prognostic factors have been candidates for trials evaluating combined modality therapy with fewer chemotherapy cycles, further reduction in radiation therapy (RT) fields or doses or even chemotherapy alone.(7,8) In contrast, for patients with unfavorable early stage HL, further intensifications of treatment have been tested.(9)

At Stanford, all patients with stage I-IIA non-bulky HL, regardless of other risk factors, have been treated uniformly with an abbreviated Stanford V combined modality therapy regimen since 1995.(10,11) The objective of this report is to apply the adverse risk factors, as defined by the EORTC, GHSG, and GELA, to our patients with non-bulky stage I-IIA HL and determine if these risk factors have prognostic value for patients treated with Stanford V chemotherapy and involved field irradiation.

Methods

Patient Selection

Patients with stage I or IIA biopsy proven HL and non-bulky mediastinal disease, defined as a mediastinal mass ratio (MMR) $< 1/3$, were identified from our lymphoma database and included in this review. All patients received treatment at Stanford Cancer Center, Kaiser Permanente Oakland, CA or Kaiser Permanente San Jose, CA, according to our established protocols and had a minimum follow-up of two years after completion of therapy.

Patients were staged according to the Ann Arbor classification with a physical exam, blood counts and chemistries, ESR, baseline chest radiograph, and a computed tomographic (CT) scan of the chest, abdomen and pelvis.(12) More recently patients also underwent PET-CT imaging as a component of their initial staging. All results were presented at a weekly multi-disciplinary conference to define stage and protocol eligibility.

Unfavorable risk factors, as defined by the EORTC, GHSG, and GELA, were applied retrospectively to determine if they held prognostic significance for this study population. The EORTC criteria for "unfavorable" included age > 50 years, > 3 involved nodal regions, or ESR ≥ 50 (≥ 30 if B symptoms).(1,2) Unfavorable patients, as defined by the GHSG criteria, included patients with EN disease, > 2 involved nodal regions, ESR ≥ 50 (≥ 30 if B symptoms). The GELA criteria for "unfavorable" were a modification of the IPS for advanced HL and included age > 45 years, male gender, any EN disease, hemoglobin ≤ 10.5 g/dL, absolute lymphocyte count ≤ 600 mg/ μ L, elevated ESR or B symptoms.(3)-(4)

Treatment

All patients were treated on protocols with a modification of the Stanford V regimen for advanced disease in which the duration of Stanford V chemotherapy was reduced from 12 to

8 weeks.(10,11) One to three weeks after completion of chemotherapy, RT to involved fields (IFRT) was delivered to 30 or 20 Gy according to two sequential protocols.(13) IFRT did not conform strictly to the Ann Arbor designated regions but followed institutional guidelines for field design. For example, upper portions of the neck were treated only if clinically involved and mediastinal fields extended no more than 5 cm inferior to the initial extent of disease. However, when the mediastinum was involved the bilateral hilar and bilateral medial supraclavicular regions were always included. The appropriate RT fields were defined before starting chemotherapy and were based on prechemotherapy physical exam and imaging studies. Following the completion of therapy patients were evaluated every 12 weeks during years 1 and 2, every 6 months during years 3 - 5, and annually thereafter. The routine evaluation included a clinical exam, laboratory studies (complete blood count, serum chemistries, and ESR), and a chest x-ray. Imaging studies (CT or PET-CT scans) were done at completion of chemotherapy, at follow-up 2 to 3 months after completion of RT, end of year 1, and end of year 2. All relapses were confirmed by biopsy.

Statistical Design

Freedom from progression (FFP) was calculated as time from the start of treatment to documented progression of disease, relapse or last follow-up. Overall survival (OS) was calculated as the time from start of treatment to death from any cause or last follow-up. FFP and OS curves were estimated by the Kaplan and Meier method.(14) Tests of statistical significance in the comparison of survival curves were calculated using the log rank statistic.

Results

From 1995-2003, 101 patients with favorable early stage HL (stage I-IIA +/- E, non-bulky) were identified. The median age was 30 years (range 17-59 years). The characteristics of these patients are shown in Table 1.

All 101 patients received 8 weeks of Stanford V chemotherapy, followed by either 30 Gy (n=84) or 20 Gy (n=17) IFRT depending on the protocol in effect on the date of assignment. At a median follow-up of 8.5 years (range 33 -111 months), the freedom from progression (FFP) was 94% and overall survival (OS) 97%, (Figure 1).

Outcome according to sub-categorization by the GHSG: Unfavorable factors included any EN disease, >2 lymph node regions involved, ESR ≥ 30 or ≥ 50 if no B symptoms were present.(2) According to these criteria, 46 of the 101 patients (45%) would be considered to be favorable and 55 (55%) unfavorable. In comparing these two cohorts, a significant difference was seen for FFP (100% versus 89% at 10 years, $p=0.02$; 0/46 relapses in the favorable group versus 6/55 in the unfavorable group). No difference was observed for OS (97% versus 96% at 10 years) (Figure 2a and b).

Outcome according to sub-categorization by the EORTC: Unfavorable factors included age ≥ 50 , >3 lymph node regions involved, ESR ≥ 30 or ≥ 50 if no B symptoms were present.(1) When these criteria were applied, 68 patients (67%) were defined as favorable and 33 patients (33%) as unfavorable. No statistically significant differences in outcome were observed between the favorable and unfavorable groups for either FFP (97% versus 88%, $p=0.07$; 2/68 relapses in the favorable group versus 4/33 in the unfavorable group) or OS (98% versus 94% $p=ns$) (Figure 3a and b).

Outcome according to sub-categorization by the GELA criteria: Unfavorable factors for the GELA (available in 99 patients) included age ≥ 45 , male gender, EN disease, hemoglobin ≤ 10.5 g/dL, absolute lymphocyte count ≤ 600 mg/ μ L, an elevated ESR and B symptoms.(3) According to these criteria, 61% of our patients (61 of 99) would have been considered to be

unfavorable. No significant differences were seen in outcome for FFP (94% versus 93%) or OS (97% versus 96%; relapse in 1/38 versus 5/61) (Figures 4a and b).

Relapses

Six of the 101 patients in this study group relapsed. All 6 had unfavorable disease defined by one or more of the European classifications (Table 2). The median time to relapse was 19 months (range 15 to 48 months). Four of the six relapses were in the RT field and in one patient also at a distant site. The latter patient with relapse in an irradiated site as well as at a distant site was a 44 year-old man with stage IIA disease who relapsed in the mediastinum (previously irradiated) and additionally had peripancreatic, splenic, and bone (vertebral) disease (distant sites). A single patient who relapsed only at a distant site, was a 42 year old woman who had received mediastinal irradiation and had progressive disease in the abdomen (retroperitoneal and portacaval nodes).

Of the six patients with relapsed disease, four were considered unfavorable by the EORTC criteria, all six by GHSG criteria and five by the GELA criteria. None of the patients identified as favorable by the GHSG or GELA relapsed, whereas two patients in the EORTC favorable group relapsed. The distribution of risk factors among relapsed patients is shown in Table 2. Among these 6 patients, all were younger than 45, three were male, all six had >2 nodal sites involved, 1 had >3 sites involved, and 3 had ESR ≥ 50 . None of the patients had EN disease. Five patients received salvage chemotherapy followed by autologous transplant and one other was treated with chemotherapy alone. Secondary therapy was successful in five of the six patients. There were 3 deaths in the total cohort of 101 patients: one from progressive disease, one transplant-related, and one due to metastatic colon cancer.

Discussion

At Stanford, as at many institutions in North America, patients with stage I-IIA Hodgkin lymphoma are defined as having “favorable” or “unfavorable” presentations based only upon the absence or presence of bulky mediastinal adenopathy (MMR $>1/3$). According to these criteria, 101 patients with favorable presentations of stage I-IIA were treated with abbreviated (8 weeks) Stanford V chemotherapy followed by IFRT to 20 or 30 Gy. An excellent outcome was achieved, with a FFP of 94% and an OS of 97% at a median of 8.5 years of follow-up. Only 6 of the 101 patients relapsed, of whom 5 were effectively salvaged by secondary therapy.

In Europe, factors in addition to bulk have been used to further classify patients with stage I-II disease as “unfavorable” for the purpose of stratification in clinical trials.^(6,15) These factors include ESR, age, number of sites of disease, EN disease and elements of the IPS. When these stratification factors were applied to our stage I-IIA patients with a MMR $< 1/3$, more than 50% were identified as having “unfavorable” presentations according to the GHSG or GELA criteria and one-third according to the EORTC criteria. Thirty three to 61% of our patients would have been eligible for and treated on “unfavorable” disease protocols in Europe. Despite their “unfavorable” characteristics, all were treated with an abbreviated chemotherapy regimen (Stanford V for 8 weeks), with reduced dose IFRT, and enjoyed an excellent overall outcome.

The current goal in the treatment of HL patients is to identify the minimum treatment required to cure patients with favorable disease and to intensify treatment (without significant increment in toxicity) for patients with advanced disease. Patients who have an intermediate prognosis are actually a blend of these two and different strategies may be appropriate. This group is quite heterogeneous. Patients who have large mediastinal adenopathy may have an increased risk of local relapse if local treatments such as RT are

reduced, whereas patients who have an elevated ESR or multiple sites of disease may be at a greater risk for systemic relapse when chemotherapy is abbreviated. In this context, a one “size” approach to management based on different prognostic factors may not be appropriate for all patients.

At Stanford, patients with stage I-IIA HL without a large mediastinal mass were treated with abbreviated chemotherapy (8 weeks) plus IFRT. The overall outcome was excellent. Applying the criteria of the GHSG or EORTC, we could identify a less favorable group of patients with a slightly inferior FFP. However, the FFP of these “unfavorable” patients was similar to that reported by the GHSG and EORTC for patients treated on their recent trials for intermediate prognosis or unfavorable disease (GHSG HD11 and HD14; EORTC H9U) which included longer duration and higher dose chemotherapy than we employed on these patients.(6,15) No impact on OS was observed by application of the European criteria, since nearly all patients who relapsed were salvaged successfully.

With respect to FFP in our cohort, the GHSG criteria were the most discriminating, with the EORTC criteria faring only slightly worse. In contrast, the GELA scoring system was the least discriminatory, suggesting that laboratory factors adapted from the IPS for advanced disease are not applicable to this patient population.(3,4) Laboratory abnormalities used in the IPS were seen only rarely in our patients. This is consistent with observations of the GHSG reporting that the IPS for advanced HL had only modest predictive power in patients with “unfavorable” presentations of early stage HL.(5) Age is a factor considered “unfavorable” by EORTC (> 50 years) and GELA (>45 years). Less than 10% of our patients were ≥ 45 years. This may partially account for why the latter two stratification criteria are not as discriminatory as those employed by the GHSG.

The obvious question that arises is whether initial identification of this small group of patients at slight increase for relapse is important. Historically, the EORTC and GHSG prognostic factors were used to determine whether a staging laparotomy was required and whether radiotherapy alone versus combined modality therapy should be used. These prognostic classifications led to risk-directed approaches and were the basis of patient selection. In the current era with modern imaging techniques, laparotomy is no longer used nor is radiotherapy alone an accepted form of therapy; therefore, the utility of the various prognostic factors is debatable. In our experience, the majority of patients (90-95%) had excellent outcomes despite some unfavorable features. If we had applied the criteria of the GHSG, for example, 55 patients may have been treated more aggressively, and have been exposed to greater risks for toxicity. However, it is not clear that more aggressive treatment, at least as has been tested by the GHSG and EORTC, would have averted these relapses, since our overall results among these 55 patients were similar to those achieved in the GHSG HD11 and HD14 and EORTC H9U trials. In addition, nearly 90% of patients with these unfavorable factors would have been treated more intensively than necessary.

An alternative to intensification of treatment for all patients is selective intensification based upon early response criteria. Early documentation of CR by CT or PET has been shown to have predictive value in a number of studies.(7,16) Currently, there are prospective trials that have been initiated in Europe and the United States employing a risk adapted approach that tailors therapy based on interim PET scanning.(17) Of note, the definition of risk factors for early stage disease varies considerably across these studies and interpretation of results will need to take into account these variables.

Recently gene-expression profiling has identified a gene signature of tumor-associated macrophages that is significantly associated with primary treatment failure. An increased number of CD68+ macrophages was correlated with a shortened PFS and a decreased

disease-specific survival.(18) Additionally the absence of an elevated number of CD68+ cells in patients with limited-stage disease defined a very favorable subgroup of patients with a long-term disease-specific survival of 100%. These results need confirmation in other data sets and if validated could potentially be used as a biological tool for risk stratification of patients.

In conclusion, our data (albeit a small sample size) suggest that for patients with stage I/IIA non-bulky HL, outcomes are excellent after treatment with abbreviated Stanford V chemotherapy and IFRT, with a FFP of 94% and OS of 97% at 10 years. Using the additional stratifications employed by the GHSG, EORTC, and GELA, we were unable to identify a cohort of patients at such a great risk for relapse that intensification of this therapy was warranted. Eventually prospective trials of a risk-adapted strategy with early response indicators or emerging biomarkers may ultimately provide the answer to the identification of patients with stage I-IIA non-bulky HL who may benefit from additional intensification of therapy.

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Figure 1. Outcome of patients treated with abbreviated Stanford V + RT At a median follow-up of 8.5 years, the FFP was 94% (solid line) and OS was 97% (dashed line).

Figure 2. Outcome according to GHSG criteria

(Solid line: favorable patients, dashed line: unfavorable patients)

2 a: FFP

2 b: OS

Figure 3. Outcome according to EORTC criteria

(Solid line: favorable patients, dashed line: unfavorable patients)

3 a: FFP

3 b: OS

Table 1

Characteristics of study patients (n=101)

Patient Characteristics	Number of patients (%)
Stage I	25 (25%)
Asymptomatic (no B symptoms)	101 (100%)
Males	56 (55%)
Nodal sites >2	46 (46%)
Nodal sites > 3	17 (17%)
ESR $\geq$ 50	14 (14%)
Sites $\geq$ 10 cm	7 (7%)
Mediastinal disease $\geq$ 10 cm	2 (2%)
Nodal disease $\geq$ 10 cm	5 (5%)
RT dose: 30 Gy	84 (83%)
RT dose: 20 Gy	17 (17%)
Age $\geq$ 45 years	8 (8%)
Age $\geq$ 50 years	4 (4%)
Extranodal disease	4 (4%)
Hemoglobin $\leq$ 10.5 gm/dL	2 (2%)

Table 2

Risk factors in 6 relapsed patients categorized as “unfavorable”

Patient	EORTC (# factors)	GHSG (# factors)	GELA (# factors)
1	-(0)	> 2 nodal sites (1)	Male (1)
2	ESR (1)	ESR, >2 nodal sites (2)	ESR (1)
3	> 3 nodal sites (1)	> 2 nodal sites (1)	Male (1)
4	ESR (1)	ESR, >2 nodal sites (2)	Male, ESR (2)
5	ESR (1)	ESR (1)	ESR, Hb (2)
6	-(0)	> 2 nodal sites (1)	-(0)

Legend:

EORTC: European Organization of Research and Treatment of Cancer

GHSG: German Hodgkin Study Group

GELA: Groupe d'Etudes des Lymphomes de l'Adulte