Limited-Stage Disease: Optimal Use of Chemotherapy and Radiation Treatment

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In the early years of treatment for limited-stage Hodgkin lymphoma there was an understandable focus on disease elimination. This has been replaced by concerns about the amount and balance of different therapies and eventually, as cure rates improve, a desire to individualize management based on risk factors at presentation and response to initial treatment. In limited stage Hodgkin lymphoma, early success was obtained with wide field radiotherapy but later combined modality approaches were employed to overcome the problem of out of field radiotherapy relapses. The acute and delayed toxicity of alkylating agent based therapies led to their replacement with ABVD and concerns about the late toxicity of radiotherapy resulted in smaller field sizes being first assessed in clinical trial and later introduced into clinical practice. The current standard of care of 3 or 4 cycles of ABVD followed by involved-field radiotherapy in clinically staged patients is the culmination of years of work involving many thousands of patients taking part in clinical trials.

Our current focus is on the role of PET imaging and whether a response-adapted approach guided by PET can individualize therapy such that radiotherapy and its attendant late toxicity that impacts on future quality of life and survival can be avoided altogether in a subset of patients.

Introduction

In limited-stage disease (stages I and II), Hodgkin lymphoma (HL) can be cured in the majority of patients by a variety of treatments used on their own or in combination. This being so our challenge for the next decade is to develop optimized approaches that focus on delivering that amount and mix of therapies to individual patients that maximizes the prospects for cure and minimizes toxicity—especially late toxicity that has an impact on future quality of life and survival.

Use of Radiotherapy Alone

In the early days of treatment for HL, imaging for staging purposes was confined to plain radiology of the thorax and lymphangiography to assess the abdomen and pelvis and therapeutic options were limited to radiotherapy and MOPP (mustine, vinblastine, vincristine [Oncovin], prednisolone) or MOPP-like chemotherapies. On the basis that lymphangiography had low levels of sensitivity for detecting disease in upper abdominal lymph nodes and the spleen, so-called staging laparotomies were routinely performed in patients with disease apparently confined to supra-diaphragmatic sites after abdomino-pelvic lymphangiography. During this procedure, lymph nodes and the liver were biopsied and a splenectomy was performed. If none of these tissues showed histological evidence of HL, the patient was said to have pathological stage I or II disease (depending on the number of nodal sites involved) and wide-field radiotherapy alone was employed.

Because it was known that HL is characterized by spread to contiguous nodal sites, "mantle field" radiotherapy encompassing all nodal sites above the diaphragm was a commonly recommended treatment. The mantle field of radiation extended cranio-caudally from the level of the cheek (zygoma) to the xiphisternum and laterally to incorporate both axillae. Lead blocks to shield the lungs were employed, but nevertheless some pulmonary tissue was irradiated and direct and scatter radiation was also delivered to the heart, breasts and thyroid gland, the coronary arteries and great vessels in the thorax and neck.

Early Combined Modality Treatment

This wide-field radiotherapy-only approach undoubtedly resulted in many cures. It was increasingly recognized, however, that despite pathological staging designed to identify patients with occult abdomino-pelvic disease for whom local treatment was inappropriate, disease relapse occurred in approximately 30% of patients, with most recurrences occurring outside the irradiation field. In other words, pathological staging was an insufficiently sensitive technique for the detection of very low volume abdomino-pelvic disease. Moreover, because it was a procedure associated with some immediate mortality (hemorrhage, pulmonary embolism, sepsis) and morbidity (wound dehiscence), chemotherapy was delayed by several weeks for those who needed it and patients, most of whom were young, were left with a cosmetically unattractive scar. Finally and especially in the youngest patients, splenectomy was found to be as-

sociated with a greatly increased risk of fatal septic shock related to infection with *Streptococcus pneumoniae* and *Haemophilus influenzae*.[1] Pre-operative immunization against these organisms and lifelong prophylaxis with penicillin became routine, but it was clear that an alternative approach was desirable.

In terms of reducing the risk of out-of-field relapse after mantle-field radiotherapy alone, the potential benefits of adjuvant chemotherapy following radiotherapy (combined modality treatment) have been investigated in randomized clinical trials. These showed that 6 cycles of MOPP or MOPP-like chemotherapies improved relapse-free survival but there was no difference in overall survival, indicating that relapse after radiotherapy alone was successfully salvaged by chemotherapy.[2] Furthermore, the improvement in relapse-free survival associated with adjuvant chemotherapies of the MOPP type was bought at the undesirable expense of high rates of toxicity including severe emesis (in an era when effective anti-emetics were not available), permanent azoospermia in males, premature menopause in females and secondary myelodysplasia/acute leukemia in both sexes. These toxicities would, of course, have been confined to only a minority of patients (those that relapsed) if radiotherapy alone had been used as a stand-alone first-line treatment.

So, an adjuvant or neo-adjuvant chemotherapy capable of delivering improved relapse-free survival resulting from elimination of occult disease not encompassed by radiotherapy but associated with less toxicity than MOPP like therapies was required. Researchers at Stanford University showed that 6 cycles of the monthly VBM (vinblastine, bleomycin, methotrexate) regimen used in combination with regional radiotherapy was superior to subtotal lymphoid irradiation (STLI) alone in pathological stages IA and IIA (plus a few patients with pathological stages IB, IIB and IIIA) and produced far less toxicity than MOPP used in a similar setting.[3] In a subsequent trial involving 78 patients with clinical stages IA and IIA (staging laparotomy not performed), the outcomes following STLI and VBM plus involved-field radiotherapy (IFRT) were comparable.[4]

As a result of clinical trials in advanced HL, the doxorubicin-containing ABVD regimen (doxorubicin, bleomycin, vinblastine, dacarbazine) was, however, becoming established as standard first-line treatment in many countries, but the question was how many cycles of treatment were required, how large should the associated radiation field be and what dose of radiation should be delivered.

Identifying Risk Groups and Using These to Direct Therapy

Early on the EORTC identified features at presentation that allow patients to be stratified into more favorable or less favorable prognostic groups. The very favorable group (6% of total) comprised female patients with clinical stage IA, age < 40 years, ESR < 50, and lymphocyte-predominant or nodular sclerosing histology. The unfavorable group (49% of total) comprised patients aged ≥ 50 years with clinical stage II and 2 to 5 involved nodal areas, if no B symptoms ESR ≥ 50 or with B symptoms ESR ≥ 30. The intermediate group (45% of the total) consisted of all other patients.[5] These prognostic groups were used to determine whether a staging laparotomy was performed and whether radiotherapy alone or combined modality treatment were employed. This risk-directed approach (as distinct from a response-adapted treatment that came later) was a very important development in the management of early stage HL and was the basis of patient selection in their subsequent trials.

In their H6 twin trials, the EORTC made the important observation that in favorable patients (H6F, see **Table 1**) outcome was similar in pathologically staged (who received STLI if laparotomy negative and mantle-field radiotherapy and chemotherapy if laparotomy positive) and clinically staged patients (who received STLI and splenic radio-

Table 1. Criteria for defining risk groups in stages I/II Hodgkin lymphoma.

Trial group	Risk group	Criteria
EORTC	Favorable	One or two nodal areas *and* No mediastinal bulk (mass > 0.35 of thoracic diameter at level of D5-6) *and* In the prescence of B symptoms, ESR < 30 *or* in the absence of B symptoms, ESR < 50
	Unfavorable	Any of the above risk factors present
GHSG	Favorable	One or two nodal areas *and* No mediastinal bulk *and* No extra-nodal disease *and* In the prescence of B symptoms, ESR < 30 *or* in the absence of B symptoms, ESR < 50 Age 75 years or less
	Unfavorable	Any of the above risk factors present
NCI (Canada) and ECOG	Exclude high risk	Bulky mediastinal involvement *or* Intra-abdominal disease
	Exclude low risk	Stage IA with single node involved in high neck or epitrochlear regions only *and* Lymphocyte predominant or nodular sclerosing histology *and* Bulk < 3 cm *and* ESR < 50
	Remainder categorized as favorable or unfavorable.	
	Unfavorable patients have *any* of	Age ≥ 40 ESR ≥ 50 Mixed cellularity or lymphocyte-depleted histology ≥ 4 sites of disease

therapy).[6] In the unfavorable group (H6U, see **Table 1**), patients were randomized between either MOPP or ABVD chemotherapies given either side of mantle-field radiotherapy (3 cycles before and 3 cycles after). Here the ABVD arm produced superior results in terms of freedom-from-progression rate (88% vs 76% at 6 years, $P = .01$) but there was no difference in survival (91% vs 85%, $P = .22$). Hematologic toxicity causing treatment discontinuation and gonadal toxicity were greater with MOPP but impairment of pulmonary function was observed more frequently after ABVD. The authors concluded that (a) staging laparotomy could be avoided in favorable patients before STLI and (b) ABVD was the choice of chemotherapy to be used in combination with mantle field radiotherapy in unfavorable patients.

The Move Towards Using Less Radiotherapy in Combination with Chemotherapy

In their HD7 trial[7] the German Hodgkin Study Group (GHSG) showed in 650 patients that 2 cycles of ABVD followed by extended-field radiotherapy (EFRT) was superior to EFRT alone in clinical stages I-IIB. In the subsequent HD8 trial,[8] 1204 patients with stages I and II and risk factors (one or more of bulky mediastinal mass, extra-nodal disease, massive splenic involvement, ESR ≥ 50 in the absence of B symptoms, ESR ≥ 30 in the presence of B symptoms, more than 2 sites of nodal involvement) were randomized between 2 cycles COPP (cyclophosphamide, Oncovin [vincristine], procarbazine, prednisolone)/ABVD followed by either 30 Gy of radiation to an extended field plus 10 Gy to bulk or 30 Gy to an involved field plus 10 Gy to bulk. Apart from more acute hematological, gastrointestinal and mucosal toxicity after extended-field radiotherapy, there was no difference between the trial arms in terms of complete response rates, freedom-from-treatment failure and overall survival, leading to the conclusion that when combined with effective chemotherapy a reduction in field size from extended to involved is entirely appropriate.

In terms of radiotherapy dose, the GHSG HD1 trial recruited patients in stage I-IIIA with unfavorable features; these patients received 2 cycles COPP/ABVD chemotherapy followed randomly by either 20 Gy or 40 Gy of extended-field irradiation to non-bulky sites.[9] In the succeeding HD5 trial a similar group of patients received the same chemotherapy as in HD1 plus 30 Gy extended-field irradiation.[10] In both trials bulky sites were irradiated to 40 Gy. Results in both trials suggested no relevant radiotherapy dose effect exists in the range of 20 to 40 Gy following 4 cycles of modern chemotherapy, indicating that doses of more than 30 Gy were no longer appropriate.

Further Evolution of Combined Treatment

In a trial from Paris involving 335 patients it was shown that, when combined with MOPP chemotherapy, there was no significant difference in disease-free or overall survival between patients receiving involved-field or extended-field radiotherapy.[11] In another randomized trial, this time from Milan,[12] 140 patients with IA and IIA disease were treated with 4 cycles ABVD followed by either STLI and splenic irradiation or involved-field RT. After prolonged follow-up (median of 116 months), 93% patients following STLI and 94% patients following IFRT are continuously disease free although because of the small numbers, statistical power to test for non-inferiority of IFRT compared with STLI is not available.

In follow-up studies to HD8 the GHSG have compared 4 cycles baseline BEACOPP with 4 cycles ABVD followed by either 30 or 20 Gy of radiation to an involved field in early stage unfavorable patients (HD11 study) and in the HD 14 study 2 cycles of escalated BEACOPP followed by 2 cycles ABVD is being compared to 4 cycles ABVD followed in both arms by 30 Gy IFRT. Both are building on the results obtained with BEACOPP in advanced disease, although there are obvious concerns about toxicity especially in the setting of limited-stage disease where overall results are extremely good and the current emphasis is on attempts to de-escalate rather than escalate treatment wherever possible.

In an important meta-analysis published in 1998, 1974 patients in 8 randomized trials comparing more versus less radiotherapy and 1688 patients in 13 randomized trials of radiotherapy plus chemotherapy versus radiotherapy alone were studied.[13] The findings of this study were that more extensive radiotherapy and the addition of chemotherapy to radiotherapy produced a large effect on disease control but only a small non-significant effect on overall survival. However, none of the of the studies analyzed involved ABVD alone (one involved alternating COPP/ABVD), and because of relatively short follow-up it was not possible to exclude a moderate but important survival benefit associated with the addition of chemotherapy. What was clear, however, is that a reduction in radiotherapy field size down to involved field has little if any impact on patient survival, and the authors made the important point that less-extensive radiotherapy may in the long term result in better survival as the sequelae of this treatment are avoided.

Chemotherapy Alone for Early Stage Disease

In view of the risks associated with radiotherapy, is a chemotherapy-only option appropriate for patients with early-stage HL? In a trial undertaken by NCI Canada and ECOG,14,399 patients were stratified into 2 cohorts; unfavorable (have any of age ≥ 40, ESR ≥ 50, mixed cellularity or lymphocyte-depleted histology, ≥ 4 sites of disease) or favorable (none of the preceding factors). Patients were then randomized to receive either a treatment that includes radiotherapy (STLI for the favorable cohort or 2 cycles ABVD plus STLI for the unfavorable cohort) or ABVD (between 4 and 6 cycles depending on response). Freedom-from-dis-

ease progression at 5 years was superior in those patients receiving radiation (93% vs 87%, $P = .006$), a difference due to reduced levels of disease control in the unfavorable cohort receiving ABVD alone (95% vs 88%, $P = .004$). There was, however no difference in overall survival with the advantage in freedom from progression associated with radiotherapy offset by deaths due to causes other than progressive HL or acute treatment-related toxicity. It may be premature to exclude a benefit in overall survival, since radiation-induced toxicity occurs late, and this trial was reported with 5-year follow-up but was powered to show overall survival benefit at 12 years.

Two other recent studies address this topic. The first from Memorial Sloan-Kettering involved 152 patients randomized between ABVD alone and ABVD plus irradiation with no difference observed at 5 years between trial arms in terms of both FFP and overall survival.[15] The second, from Spain, was a single arm Phase II study[16] that showed a progression-free survival of 88% for 80 patients with non-bulky disease after a median follow-up of 78 months, a result identical to that of the NCI Canada trial but with longer follow-up.

There is need for caution, however. The EORTC had to prematurely close their H9F trial because of an excessive number of relapses occurring in a chemotherapy-only arm.[17] The chemotherapy in question was a reduced-intensity regimen, EBVP (epirubicin, bleomycin, vinblastine, prednisolone) rather than the better known ABVD, but it is clear that very careful patient selection is required if radiotherapy is not to be dropped from treatment inappropriately.

Response Adapted Therapy and the Role of FDG-PET Imaging

Given the interest in a chemotherapy-only approach to the treatment of limited-stage HL associated with concerns about a reduction in disease control associated with not giving radiotherapy, a key question is whether FDG-PET imaging can identify patients in whom initial chemotherapy has eradicated disease. So-called response-adapted strategies depends on the sensitivity of PET at detecting residual disease and, if successful, would complement the initial stratification of patients based on pretreatment prognostic factors. A randomized trial in the UK is addressing the issue of PET as a reliable biomarker of disease in patients with stages IA and IIA HL above the diaphragm. All eligible and consenting patients receive 3 cycles of standard ABVD followed by a PET scan (presuming that complete or partial remission measured by conventional CT criteria has been achieved). Those who are PET "negative" (no FDG uptake) as determined by central core lab review are randomized between IFRT and no further treatment. Those who are PET "positive" receive a cycle of ABVD and IFRT.

With 320 PET-negative patients randomized in this trial a difference of 10% in progression-free survival between the randomized arms can be excluded with 90% power (statistics section, trial protocol). A key question, though, is whether excluding such a difference will be practice changing. In a recent survey of international experts in the field, excluding a smaller difference (of between 6% and 7%) was favored by the majority and there are plans to extend recruitment to take account of these findings.

An additional important point here is that even if there is some initial loss of disease control associated with PET false-negative patients not receiving radiotherapy, this may ultimately lead to overall better outcomes (less morbidity and mortality from second cancers and cardiovascular disease) than if the whole population were irradiated and there were fewer episodes of relapse. This balancing of competing risks is central to the concept of optimizing treatment in limited-stage HL.

Conclusion

The evolution of treatment for limited-stage HL over many years is a paradigm for the treatment of cancer in general. An early and understandable focus on disease elimination (perhaps at any cost) has been replaced by concerns about the amount and balance of different therapies and, eventually, as cure rates improve, a desire to individualize management based on risk factors at presentation and response to initial treatment. In limited stage HL, early success was obtained with wide-field radiotherapy but later combined modality approaches were employed to overcome the problem of out-of-field radiotherapy relapses. The acute and delayed toxicity of alkylating agent–based therapies led to their replacement with ABVD, and concerns about the late toxicity of radiotherapy resulted in smaller field sizes being first assessed in clinical trial and later introduced into clinical practice. The current standard of care of 3 to 4 cycles of ABVD followed by IFRT in clinically staged patients is the culmination of years of work involving many thousands of patients taking part in clinical trials.

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References

1. Donaldson SS, Moore MR, Rosenberg SA, et al. Characterization of postsplenectomy bacteremia among patients with and without lymphoma. N Engl J Med. 1972;287:69-71.
2. Anderson H, Deakin DP, Wagstaff J, et al. A randomized trial of adjuvant chemotherapy after mantle radiotherapy in supradiaphragmatic Hodgkin's disease PS IA-IIB: a report from the Manchester lymphoma group. Br J Cancer. 1984;49:695-702
3. Horning SJ, Hoppe RT, Hancock SL, et al. Vinblastine, bleomycin and methotrexate: an effective adjuvant in favorable Hodgkin's disease. J Clin Oncol. 1988;6:1822-1831.
4. Horning SJ, Hoppe RT, Mason J, et al. Stanford-Kaiser Permanente G1 study for clinical stage I to II Hodgkin's disease: subtotal irradiation versus vinblastine methotrexate and bleomycin chemotherapy and regional irradiation. J Clin Oncol. 1997;15:1736-1744.
5. 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: 1962-1987. Blood. 1989;73:47-56.
6. Carde P, Hagenbeek A, Hayat M, et al. Clinical staging versus laparotomy and combined modality with MOPP versus ABVD in early stage Hodgkin's disease: the H6 twin randomized trials from the European Organization for Research and Treatment of Cancer Lymphoma Cooperative group. J Clin Oncol. 1993;11:2258-2272.
7. 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. 2007;25:3495-3502.
8. 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;21:3601-3608.
9. Diehl V, Loeffler M, Pfreundschuh M, et al. Further chemotherapy versus low dose involved field radiotherapy as consolidation of complete remission after six cycles of alternating chemotherapy in patients with advanced Hodgkin's disease: German Hodgkins Study Group (GHSG). J Clin Oncol. 2003;21:3601-3608.
10. Loeffler M, Diehl V, Pfreundschuh, et al. Dose-response relationship of complementary radiotherapy following four cycles of combination chemotherapy in intermediate stage Hodgkin's disease. J Clin Oncol. 1997;15:2275-2287.
11. Zittoun R, Audebert A, Hoerni B, et al. Extended versus involved fields irradiation combined with MOPP chemotherapy in early clinical stages of Hodgkin's disease. J Clin Oncol. 1985;3:207-214.
12. Bonadonna G, Bonfante V, Viviani S, et al. ABVD plus subtotal nodal versus involved-field radiotherapy in early stage Hodgkin's disease: long term results. J Clin Oncol. 2004;22:2835-2841.
13. Specht L, Gray RG, Clarke MJ, Peto R. Influence of more extensive radiotherapy and adjuvant chemotherapy on long term outcome of early stage Hodgkin's disease: a meta-analysis of 23 randomized trials involving 3,888 patients. J Clin Oncol. 1998;16:830-843.
14. 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. 2005;23:4634-4642.
15. 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;104:3483-3489.
16. Dominguez AR, Márquez A, Gumá J, et al. Treatment of stage I and II Hodgkin's lymphoma with ABVD chemotherapy: results after 7 years of a prospective study. Ann Oncol. 2004;15:1798-1804.
17. Eghbali H, Price P, Creemers GY, et al. Comparison of three radiation doses levels after EBVP regimen in favorable supradiaphragmatic clinical stages (CS) I-II Hodgkin's lymphoma (HL): preliminary results of the EORTC-GELA H9-F trial [abstract]. Blood. 2005;106. Abstract #814a.