Hodgkin Lymphoma

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The Management of Patients with Limited-Stage Classical Hodgkin Lymphoma

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The term limited-stage Hodgkin lymphoma refers to those patients with stage I-II disease and an absence of bulky disease. Among those patients with classical Hodgkin lymphoma, approximately one-third of patients will fall into this category. As long-term disease control can now be anticipated in more than 90% of these patients, management strategies must increasingly address the need to reduce the long-term treatment-related risks. Current treatment options include use of combined modality therapy that includes an abbreviated course of chemotherapy and involved-field radiation or treatment with chemotherapy, currently consisting of ABVD, as a single modality. The choice of treatment between these two options involves specific trade-offs that must balance issues of disease control against long-term risk of late effects.

The objectives of this review are to evaluate the literature that shapes the current treatment of patients with limited-stage classical Hodgkin lymphoma and to offer practical guidance in their management. The review will be divided into sections dealing with parameters that define limited-stage disease, the evolution of data that have determined treatment practices, the late effects of therapy, an analysis of the current major treatment options and finally, issues of follow-up and survivorship. The estimated incidence of new cases of Hodgkin lymphoma in the United States in 2006 is 7800 with an estimated number of deaths of 1800.[1] The resulting mortality-to-incidence rate ratio of 0.19 reflects both the high potential of curability and the knowledge that this potential is not achieved in a significant proportion of patients. Given the potential to cure the disease, and the expectation of fewer unrelated competing risks of mortality in this young patient population (median age, 37 years[2]), there is particular importance in providing therapies that balance the issues of durable disease control with those of long-term treatment-related toxicity.

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Defining Limited-Stage Hodgkin Lymphoma

The Ann Arbor staging classification,[3] including the modification resulting from the Cotswolds meeting,[4] is shown in **Table 1**. Current management strategies for Hodgkin lymphoma usually involve collapsing this classification into two or three categories. In North America, cooperative group trials have defined limited-stage as those patients with clinical stage I-IIA and an absence of bulky (≥ 10 cm) disease. Patients with stage IIB or those with stage I-II bulky disease are treated with the same protocols as those with stage III-IV disease and receive full courses of chemotherapy. Concepts tested in current clinical trials that include patients with advanced-stage disease may be based upon the prognosis of these patients as assessed by the International Prognostic Index.[5] In addition, patients who have bulky disease are considered for radiation therapy to the site of bulky disease, especially when a large mediastinal mass is present.

Cooperative group practices in Europe generally use a similar schema with considerable overlap with what would be categorized in North America as limited-stage disease and for patients with stage III-IV disease.[6] The term 'favorable early stage disease' includes patients less than 50 years old with stage I-II presentations, without B symptoms or bulky mediastinal disease, with a low erythrocyte sedimentation

Table 1. Ann Arbor staging system for Hodgkin lymphoma, including the Cotswolds modifications.

Stage	Disease Involvement
I	Single lymph node region (I) or one extralymphatic site (I_E)
II	Two or more lymph node regions, on the same side of the diaphragm (II) or local extralymphatic extension plus one or more lymph node regions on the same side of the diaphragm (II_E)
III	Lymph node regions on both sides of the diaphragm (III), which may be accompanied by local extralymphatic extension (III_E)
IV	Diffuse involvement of one or more extralymphatic organs or sites
A	No B symptoms
B	Presence of at least one of: unexplained weight loss >10% baseline during 6 months prior to staging; recurrent unexplained fever > 38°C; recurrent night sweats
X	Bulky tumor: either a single mass exceeding 10 cm in largest diameter or a mediastinal mass exceeding one third of the maximum transverse transthoracic diameter measured on a standard posterior-anterior chest radiograph

rate, and fewer than four sites of involvement. A separate category of "unfavorable early-stage" disease is defined in Europe, which includes patients with stage I-II A+B disease and one or more of the above risk factors.

The remainder of this review will deal with patients who have stage I-IIA non-bulky disease, and who we will refer to as having limited-stage disease. Providing a precise estimate from large population databases of the proportion of patients with Hodgkin lymphoma who fall into the category of limited-stage disease is not possible. Attempts are confounded by difficulties in constructing inception cohorts of patients who have undergone rigorous diagnostic staging. A best estimate is that approximately one-third of newly diagnosed patients will fall into this category.[7]

Evolution to Current Standards of Care

The management of patients with limited-stage Hodgkin lymphoma has changed dramatically over the past 15-20 years. Until the late 1980s, management included performing a staging laparotomy and splenectomy and treatment included extended field radiation. More recently, with clinical staging based on computerized tomographic (CT) imaging and the availability of less toxic and more effective systemic chemotherapy, use of combined modality therapy has led to improved results. Treatment with large radiation fields has been abandoned, since it is strongly associated with an increased risk of second cancers and cardiac late effects. It is important to recognize the principles that these advances represent; as modern imaging modalities such as positron emission tomographic (PET) scanning and combined PET-CT scanning become validated and treatment with new targeted systemic therapies evolves, further changes in treatment policies are to be expected.

The evolution of therapy over time has included four specific advances. The first was the demonstration that surgical staging was not necessary. The clinical trial best demonstrating this principle was the H6 trial of the European Organization for Research and Treatment of Cancer (EORTC), in which patients were randomized to receive treatment based upon clinical or surgical staging that included laparotomy.[8] No differences in progression-free or overall survival were detected. The second advance was the demonstration that treatment with combined modality therapy was superior to treatment with radiation therapy as a single modality. Evidence for this conclusion evolved from many studies that were included in an individual patient data meta-analysis, which demonstrated superior long-term disease control in patients receiving combined modality therapy,[9] and further evolved as a result of three randomized trials that each demonstrated that such improvement in disease control could be achieved with abbreviated courses (i.e., 2 or 3 cycles) of chemotherapy.[10-12]

The third and the most important advance was the demonstration that inclusion of chemotherapy as part of combined modality therapy allowed for a reduction in the magnitude of radiation treatment. A randomized trial conducted in Italy[13] demonstrated this principle; a comparison of combining doxorubicin (Adriamycin®), bleomycin, vinblastine and dacarbazine (ABVD) with either involved or extended fields of radiation therapy observed no differences in outcomes. In addition, the EORTC H8F trial was a landmark in demonstrating that combined modality therapy that included an abbreviated course of chemotherapy and involved field radiation therapy resulted in superior outcomes in comparison with subtotal nodal radiation therapy.[11] Validation of the ability to reduce the field of radiation has been provided by the EORTC in their H9F[14] and the German Hodgkin's Study Group (GHSG) in their HD10[15] randomized trials (**Table 2**). Preliminary results of these trials demonstrate that excellent outcomes are achieved with combined modality therapy that includes radiation to the involved-field. In addition, the concept of radiation dose has been tested in each of these trials; in the EORTC trial radiation therapy with 36 Gy was compared with 20 Gy and in the GHSG trial 30 Gy was compared with 20 Gy. In these initial reports, no differences in outcomes have yet been detected.

The fourth advance has been the testing of chemotherapy as a single modality in patients with limited-stage disease. This approach is based on the hypothesis that treatment with chemotherapy alone would be a preferable alternative as it will be associated with fewer late effects. In order to test this hypothesis, randomized trials are needed to test optimal chemotherapy in a sufficiently large sample size to permit detection of important differences, with sufficient follow-up to assess for late effects. As long-term follow-up will be required to evaluate late effects, the even-

Table 2. Recent randomized trials testing combined modality therapy that includes involved-field radiation therapy.

Trial	Chemotherapy	Radiation Therapy	Outcomes	*P* value
EORTC H9F[14]	EBVP, 6 cycles	IF 36 vs 20 Gy	4-yr EFS: 87% vs 84% 4-yr OS: 98% vs 98%	No significant differences between groups
GHSG HD10[15]	ABVD, 2 vs 4 cycles	IF 30 vs 20 Gy	Overall: FFTF 96.6% and OS 98.5% (median follow-up 2 years)	No significant differences between groups

Abbreviations: EORTC, European Organization for Research and Treatment of Cancer; GHSG, German Hodgkin's Study Group; EBVP, epirubicin, bleomycin, vinblastine, prednisone; ABVD, doxorubicin (Adriamycin®), bleomycin, vinblastine and dacarbazine; IF, involved field; EFS, event-free survival; OS, overall survival; FFTF, freedom from treatment failure

tual analyses of these trials will require that the treatment administered during the conduct of the trial be put into context with treatment that is current. A review of randomized trials testing chemotherapy alone in patients with limited-stage disease, and synopsis of potential limitations, is shown in **Table 3**. Eight randomized trials[14,16-22] testing chemotherapy alone in patients with limited-stage disease have been reported, either as specific trials or as subset analyses of larger trials. Four of these trials tested chemotherapy that has been shown to be inferior to ABVD or its equivalent[14,16-18] and thus these treatments cannot be recommended and the trials do not adequately test currently available chemotherapy as a single modality.

Of the remaining four trials that have tested chemotherapy regimens that are associated with currently achievable optimal disease control (results shown in **Table 4**), two trials[19,20] report results of subset analyses from larger trials; in both reports, differences in the event-free or overall survivals of the randomized groups were not detected. The third trial, reported by Straus,[21] was a single institution trial comparing combined modality therapy with ABVD alone in patients with stages I-II A+B and IIIA disease. The trial therefore included a more heterogeneous patient group than that currently defined as limited stage. No differences in freedom from progression or overall survival were detected but the sample size of the trial (152 patients) provided limited power to detect differences that might be clinically important.

The final trial[22] was conducted by the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) and Eastern Cooperative Oncology Group (ECOG) and included 399 evaluable patients with limited-stage disease. Patients were randomized to receive either 4-6 cycles of ABVD (the number of cycles was determined by the degree of antitumor response observed following the first 2 cycles) or to treatment that included radiation therapy. The trial was begun in 1994, and before application of current standards of combined modality therapy. Its design therefore included

Table 3. Properties of randomized trials testing chemotherapy alone in patients with limited stage Hodgkin lymphoma.

Author/ Reference	Chemotherapy/ Efficacy Equivalence to ABVD	Radiation Therapy/ Part of Combined Modality Therapy	Sample Size/ Power to Detect Important Differences	Other
Longo[16]	MOPP / no	STNI or TNI / no	106 / no	Includes Stages I-IIIA, I-IIB and patients with bulky disease
Biti[17]	MOPP / no	EF / no	99 / no	
Pavlovsky[18]	CVPP / no	IF / yes	277 / yes	Includes Stages I-IIA+B and patients with bulky disease
Noordijk[14]	EBVP / no	IF / yes	619 / yes	
Laskar[19]	ABVD / yes	Predominantly IF / yes	99 / no	Subset analysis
Nachman[20]	COPP-ABV / yes	IF / yes	215 / uncertain	Subset analysis; included pediatric patients only
Straus[21]	ABVD / yes	EF (*n* = 54) and IF (*n* = 11) in an "as treated" analysis / yes	152 / no	Includes Stages I-IIIA and I-IIB
Meyer[22]	ABVD / yes	EF / no (*n* = 64) and yes (*n* = 139)	399 / yes	

Abbreviations: MOPP, nitrogen mustard, Oncovin® (vincristine), prednisone, procarbazine; CVPP, cyclophosphamide, vinblastine, prednisone, procarbazine; EBVP, epirubicin, bleomycin, vinblastine, prednisone; COPP, cyclophosphamide, Oncovin® (vincristine), prednisone, procarbazine; ABVD, doxorubicin (Adriamycin®), bleomycin, vinblastine and dacarbazine; (S)TNI, (sub) total nodal irradiation; IF, involved field; EF, extended field

Table 4. Randomized trials comparing ABVD or regimen of equivalent efficacy alone with treatment that includes radiation therapy.

Author	Control Therapy	Experimental Therapy	Number	Disease Control Outcome*	Overall Survival*
Laskar[19]	ABVD + IF RT	ABVD	99	8-yr EFS: 97% vs 94%; *P* = 0.29	8-yr: 100% vs 98%; *P* = 0.26
Nachman[20]	COPP-ABV + IF RT	COPP-ABV	215	3-yr EFS: 97% vs 91%; *P* ns	3-yr: 100% vs 100%; *P* ns
Straus[21]	ABVD + EF RT	ABVD	152	5-yr FFP: 86% vs 81%; *P* = 0.61	5-yr: 97% vs 90%; *P* = 0.08
Meyer[22]	EF RT (favorable cohort; *n* = 64) or CMT (unfavorable cohort; *n* = 139): ABVD + EF RT	ABVD	399	5-yr FFP: 93% vs 87%; *P* = 0.006	5-yr: 94% vs 96%; *P* = 0.4

* Results reported for control group followed by experimental group
Abbreviations: ABVD: doxorubicin (Adriamycin®), bleomycin, vinblastine and dacarbazine; COPP: cyclophosphamide, Oncovin® (vincristine), prednisone, procarbazine; IF RT: involved-field radiation; EF RT: extended-field radiation; CMT: combined modality therapy; EFS: event-free survival; FFP: freedom from progression; ns: not stated

having patients stratified prior to randomization, based on a schema of prognostic factors then used for patients with limited-stage disease, in order to determine whether those allocated to the radiation arm should receive extended field radiation alone or in combination with 2 cycles of ABVD. In both the overall analysis and in a subset analysis comparing the stratum of patients who received combined modality therapy with those receiving ABVD alone, freedom from progression (FFP) was superior in patients randomized to receive radiation but no differences in overall survival were seen. With a median follow-up of 4.2 years, second cancers or cardiovascular events were observed in 8 patients randomized to chemotherapy alone and in 18 patients allocated to the radiation treatment arm. The primary objective of the NCIC CTG / ECOG trial was to test whether treatment with ABVD alone results in an improved overall survival by reducing the amount of radiation; in the eventual final analysis of the trial, the 12-year overall survivals of the randomized groups will be compared. Evaluation of FFP was a secondary objective. An appraisal of these results must take into account that a more current strategy of combined modality therapy for all patients would be expected to result in larger observed differences in FFP between randomized groups. Furthermore, the trial included extended-field radiation therapy, an approach that is no longer used. While the use of extended field radiation is unlikely to be associated with any substantial difference in FFP over involved-field radiation, there may be important risks for additional late effects associated with the more extensive radiation.

Issues of Late Effects

The study of late effects remains an important task in the management of patients with stage I-II Hodgkin lymphoma.[23] Large population-based studies showed a 21.9% actuarial risk of developing a solid tumor at 25 years after Hodgkin lymphoma diagnosis. The risk of coronary artery disease has been reported to be as high as 6% at 10 years and 10-20% at 20 years.[24] With more than 90-95% of patients cured of their disease, survival is more influenced by late mortality. It has been known for more than 20 years that the use of radiation therapy was associated with significant rates of second cancers presenting 10 or more years after treatment completion.[25] However, in the era of chemotherapy with nitrogen mustard, vincristine (Oncovin®), prednisone and procarbazine (MOPP), chemotherapy was associated with a 5% risk of almost uniformly fatal acute leukemia that occurred within 5 years of treatment, and infertility. Radiation therapy was thus a better alternative. Once the risk of leukemia and infertility were removed with ABVD chemotherapy, efforts were undertaken to enhance the use of combined modality therapy and to reduce the dose and extent of radiation. Newer studies of late effects characterized the risk further.[23-28] We now know that thoracic radiation in women treated under the age of 30 years results in a very high rate of breast cancer that approximates 30% at 30 years following treatment[25] but that this risk is much lower in women who received alkylating agent chemotherapy with no hormone replacement therapy.[27] We also know that heavy smokers after thoracic radiation for Hodgkin lymphoma have a 20 times higher risk of lung cancers while light or nonsmokers have a 7 times higher risk.[28] The dose and volume of radiation increase these risks, and newer treatment protocols that use lower radiation doses and reduced volumes should reduce the risk of second cancers.[29] Late effects of MOPP chemotherapy have been well characterized. The late toxicity of ABVD chemotherapy has still to be defined, but early reports suggest a negligible risk of leukemia and very low risk of infertility. Late cardiac toxicity is more difficult to study especially since many patients receive ABVD with thoracic radiotherapy.

Analysis of Current Treatment Options

Based on the above data, patients and physicians currently have two main options for treatment, and these options are

associated with specific trade-offs. The first treatment option is with combined modality therapy that includes 2 cycles of ABVD and radiation therapy to the involved field. Until data from the EORTC H9F and the GHSG HD10 studies mature, a reasonable radiation treatment dose is 30 Gy. The advantage of this approach is that it provides therapy that will maximize disease control, which would be expected in approximately 95% of patients. The disadvantage is that includes exposure to radiation and therefore the risk of late cardiovascular events and development of second cancers. Given advances in radiation technology, these risks may be reduced in comparison with historical cohorts, but it should be presumed that important risks would remain.

The second option is to provide therapy with ABVD alone. This treatment may result in a reduction of long-term disease control, with the magnitude of decrement estimated at about 7%, or a number needed-to-treat in order to receive benefit from radiation therapy of approximately 14. While still evolving, preliminary data suggest that patients with disease progression after receiving chemotherapy alone can achieve states of durable disease control with second-line therapy that is likely to be radiation-based.[30] The advantage of this treatment approach is the avoidance of radiation therapy and the associated late-effect risks. Balancing these options and selecting a course of therapy will require careful discussions with patients and accounting for individual preferences in the eventual choice. Two additional parameters might influence this treatment decision. The first relates to the specifics of the radiation field. Larger fields, and those that include significant portions of the mediastinum, are likely to be more associated with late-effect risks. Knowledge of this may influence how options are balanced. The second additional parameter accounts for the concept of "response-adapted" therapy. For example, in the NCIC CTG/ECOG trial, patients allocated to chemotherapy alone underwent restaging after 2 treatment cycles. Those achieving a complete response (CR) at that point received 2 more cycles for a total of 4; those not achieving a CR received 4 more cycles for a total of 6. With a median follow-up of 4.2 years, the 5-year FFP was superior in those achieving a CR after 2 cycles (95% vs. 81%; $P = 0.007$).[22] This trial predated the use of PET scanning, and recent data suggest that PET scanning during therapy may be particularly predictive of outcome in these patients.[31] Validation of the concept of response-adapted therapy is required before it can be broadly recommended and is now being formally tested in the EORTC H10 trial, which incorporates PET scanning.

Follow-up and Survivorship

Patients with Hodgkin lymphoma require special forms of extended follow-up. Within 5 years of completing therapy, the nature of this follow-up should emphasize education about prevention and detection of late effects over the detection of recurrent disease. Patients should be specifically counseled about minimizing risk factors for cardiovascular disease, smoking cessation, avoidance of sun exposure and for women who have received thoracic radiation, breast screening. The optimal follow-up protocols for patients with early stage Hodgkin lymphoma have been achieved by consensus rather than being based directly on evidence from randomized trials.[32] Given the tremendous difficulty in conducting randomized trials, clinicians may benefit from regularly referring to well-conducted consensus studies that include updates and referencing websites such as the Children's Oncology Group Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers[33] (http://www.survivorshipguidelines.org/).

Summary

Limited-stage Hodgkin lymphoma is a highly curable disease. Attention to detail is required in staging assessment, quality of treatment and assessment of response to achieve the currently achievable cure rates of more than 95%. Follow-up is directed to detecting relapse, and more importantly, to preventing, monitoring and managing the late effects of treatment.

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