



Evolving Approaches to Primary Treatment of Hodgkin Lymphoma

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Two challenges confront the clinician treating Hodgkin lymphoma today: achieving a high level of effectiveness while minimizing toxicity. At least 80% of patients can be cured with currently available chemotherapy regimens, augmented in selected patients with the addition of involved field radiation or intensified chemotherapy assisted by granulocyte growth factors or stem cell transplantation. Major late toxicity including infertility, premature menopause, cardiovascular disease and second neoplasms can be avoided in most patients if the treatment program is chosen carefully.

The extent of disease (stage) and, for advanced stage lymphoma, the presence of well-characterized prognostic factors can be established with readily available clinical, laboratory and imaging techniques. Results from carefully designed and analyzed clinical trials have identified optimal treatment approaches for patients with limited and advanced stage disease. Those with limited stage Hodgkin lymphoma should be treated with brief chemotherapy, only augmented with involved field irradiation if an early complete remission is not achieved. Most patients with advanced

stage lymphoma can be cured with an extended course of ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine). The small minority under the age of 60 years with an International Prognostic Factors Project score of 5 or greater should be considered for intensified chemotherapy. Patients known to have bulky tumor(s) (> 10 cm) at diagnosis may require adjuvant irradiation at the conclusion of chemotherapy, but its utility has not been unequivocally established and radiation should be avoided in those who achieve a complete remission, where it is known to be ineffective.

With careful selection of treatment program most patients found to have Hodgkin lymphoma today can be offered a high probability of cure and a low likelihood of major late toxicity. However, without detailed attention to the extent of lymphoma and other prognostic factors, there is as much danger of over-treatment as under-treatment. Only by thoughtfully adjusting the treatment program to the extent of disease and response to treatment can the clinician determine the optimal approach, maximizing likelihood of cure and minimizing late toxicity.

Background

In 2005 we can expect approximately 20,000 new cases of Hodgkin lymphoma to have been diagnosed in North America and Europe. The age-adjusted annual incidence of approximately 2.7 per 100,000, which stands in clear contrast with an age-adjusted annual mortality of less than 0.5 per 100,000, has declined modestly over the past 20 years. More than 90% of cases occur in adults ranging in age from 16 to 65 years with a median of approximately 35. Relatively few cases occur in the elderly or in children. This lymphoma occurs slightly more often in men and much less frequently in populations derived from eastern Asia such as the Chinese and Japanese. In central Asia the overall incidence is more similar to that in the west, but the age of diagnosis is shifted into the pediatric range. The cumulative lifetime risk of developing Hodgkin lymphoma is approximately 1 in 250 to 1 in 300 in North America.

The diagnosis of Hodgkin lymphoma is based on the recognition of Reed-Sternberg cells and/or Hodgkin cells

in an appropriate cellular background in tissue sections from a lymph node or extra-lymphatic organ, such as the bone marrow, lung or bone. Fine needle aspiration biopsy is not adequate for the diagnosis of Hodgkin lymphoma. Open biopsy is required because of the need to establish the diagnosis unequivocally and to determine the histologic subtype.

The staging system for Hodgkin lymphoma is based on clinical staging according to the Ann Arbor system with the addition of a definition of bulky disease (**Table 1**).^{1,2} The tests required to establish the correct stage are shown in **Table 2**. Staging laparotomy is not required. In North America treatment is usually designed for either limited stage disease (stage IA or IIA, low bulk [< 10 cm]) or advanced stage disease (B symptoms or bulky [≥ 10 cm] or stage III or IV). It is common in Europe to further subdivide those with limited stage into favorable and unfavorable subgroups, but the necessity for this subdivision has not been established. Once the diagnosis has been confirmed and the stage established, definitive treatment can be planned based on a series of key observations derived from carefully conducted clinical trials.

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Table 1. Modified Ann Arbor staging system for Hodgkin lymphoma.

Stage Involvement

- I Single lymph node region (I) or one extralymphatic site (I_E).
- II Two or more lymph node regions, same side of the diaphragm (II) or local extralymphatic extension plus one or more lymph node regions 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.

Symptoms

A = no B symptoms

B = presence of at least one of these:

- 1) unexplained weight loss > 10 % baseline during 6 months prior to staging
- 2) recurrent unexplained fever > 38°C
- 3) recurrent night sweats

Bulky tumor is defined as any single mass of tumor tissue exceeding 10 cm in largest diameter. The previously used definition of a mediastinal mass exceeding 1/3 of the maximum transverse transthoracic diameter measured on a standard posterior-anterior chest radiograph is obsolete in an era with widely available computed tomographic scans.

Limited Stage Hodgkin Lymphoma: Key Studies

Of the approximately 20,000 new cases of Hodgkin lymphoma diagnosed each year in the North America and Europe about 6000 to 7000 (30%) have limited-stage disease. Almost all patients with limited-stage disease can be cured, and the current challenge is to optimize treatment so that it is accomplished with the least toxicity, lowest cost and greatest efficiency. Currently available approaches can be reasonably expected to almost completely eliminate the risk of relapse and still minimize long-term toxicity and complications. A number of crucial studies have made seminal contributions to the approach to limited-stage disease and are worth examining in detail. Although more than twenty randomized trials addressed the role of chemotherapy in limited-stage Hodgkin lymphoma, most are not relevant today. Many included patients with bulky disease; some selectively employed staging laparotomy; many lacked modern generation CT scanning; and, most importantly, the chemotherapy chosen was often less effective than ABVD, the regimen that is most effective and least toxic for advanced-stage disease.³⁻⁵ Today we are most interested in data from trials based on a strategy of brief duration ABVD with or without irradiation. Such an approach eliminates any substantial risk of infertility, premature menopause or leukemia and minimizes concern about cardiopulmonary toxicity. Three groups reported the results of using brief ABVD and irradiation for clinical stage

Table 2. Required staging tests for Hodgkin lymphoma.

1. Pathology review
2. Complete history searching for B symptoms or other symptomatic problems suggesting more advanced disease
3. Physical examination for lymphadenopathy or organomegaly
4. Complete blood count plus erythrocyte sedimentation rate (ESR)
5. Serum creatinine, alkaline phosphatase, lactate dehydrogenase, bilirubin, calcium, AST, serum protein electrophoresis (including albumin level)
6. Chest radiograph, posterior-anterior and lateral views
7. CT scan of the neck, thorax, abdomen and pelvis
8. Tests that are only required for specific Hodgkin lymphoma presentations:

Test	Presentation/Condition
Bone marrow biopsy and aspiration	B symptoms or WBC < 4.0 x 10 ⁹ /L or Hgb < 120 g/L (women), 130 g/L (men) or Platelets < 125 x 10 ⁹ /L
ENT examination	Stage IA or IIA disease with upper cervical lymph node involvement (supra-hyoid)

Abbreviations: ENT, ear, nose and throat

IA or IIA non-bulky Hodgkin lymphoma in adult patients, one in Milan,⁶ another in Vancouver⁷ and, more recently, the German Hodgkin's Study Group (GHSG)⁸ (**Table 3**). The Milan trial included a randomization to involved versus extended field RT after 4 months of ABVD but has shown no difference between the two and, therefore, the results from that center have been pooled. These data make it clear that brief chemotherapy with ABVD followed by irradiation is highly effective at eradicating limited-stage Hodgkin lymphoma. Until quite recently such combined modality treatment could be considered the gold standard for limited-stage disease.

The primacy of radiation for the management of limited-stage Hodgkin lymphoma was established many years ago and rested on its clear curative potential. However, by the 1990s the realization that a substantial proportion of the excess mortality eventually experienced by patients with limited-stage Hodgkin lymphoma is closely related to the use of irradiation, which contributes to cardiovascular disease and second neoplasms arising in breast, lung, gastrointestinal tract and connective tissue,⁹⁻¹⁴ made this an important area of clinical research. By then it had become clear that chemotherapy alone might work just as well and the eventual choice between the two was more likely to reflect differences in toxicity than efficacy. With the identification of ABVD as the regimen best combining high efficacy with low toxicity,^{4,5} a test of chemotherapy

Table 3. Brief ABVD chemotherapy followed by irradiation for limited stage Hodgkin lymphoma.

	Milan	Vancouver	GHSg
Number of patients	114	170	204
Median follow-up (months)	38	42	22
Months of ABVD	4	2	2
RT field	involved or extended	involved or extended	extended
Disease free survival (%)	94	96	96
Overall survival (%)	100	97	98

Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine and dacarbazine; GHSg, German Hodgkin's Study Group; RT, radiation therapy

versus combined modality therapy for limited-stage Hodgkin lymphoma became appropriate.

The cooperative group trial comparing ABVD alone with either wide field radiation for patients with favorable prognostic factors or ABVD for two cycles followed by wide field radiation for patients with unfavorable prognostic factors conducted by the National Cancer Institute of Canada Clinical Trials Group and the Eastern Cooperative Oncology Group¹⁵ provides the information needed to justify elimination of radiation from the management of most patients with limited stage Hodgkin lymphoma (**Table 4**). Although there was a modest difference in progression-free survival, there was none in event-free or overall survival. It is particularly instructive to examine the events noted in the patients assigned to ABVD alone. The trial design called for these patients to be re-assessed after 2 cycles of ABVD. Those in complete remission completed treatment with 2 more cycles while those with less than a complete remission continued on to receive 4 more cycles for a total of 6 cycles of chemotherapy. Those patients in complete remission after 2 cycles of ABVD, who were therefore only treated with a total of 4 cycles, have a progression-free survival of 95%. With the advent of more accurate functional imaging

Table 4. ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine) alone versus either wide field radiation for patients with favorable prognostic factors or ABVD for two cycles followed by wide field radiation for patients with unfavorable prognostic factors for limited stage Hodgkin lymphoma.

	ABVD	RT or ABVD + RT	<i>p</i>
Number of patients	196	203	
5 y PFS	87	93	0.006
5 y EFS	86	88	0.06
5 y OS	96	94	0.4

Abbreviations: RT, wide field radiation; PFS, progression free survival; EFS, event free survival; OS, overall survival

such as PET scanning it is likely that the majority of patients requiring only 4 cycles of ABVD to be cured can be identified after 2 cycles of treatment, sparing them prolonged chemotherapy or radiation. This trial has established that ABVD alone is an acceptable option for patients with limited-stage Hodgkin lymphoma. Longer follow-up will be necessary to see if the goal of reducing late cardiovascular events and second neoplasms was accomplished.

Advanced-Stage Hodgkin Lymphoma: Key Studies

We have known that advanced-stage Hodgkin lymphoma can be cured with multi-agent chemotherapy for more than three decades. The first widely used multi-agent program, MOPP (mechlorethamine, vincristine, procarbazine and prednisone), produced a response rate of 80% and long-term disease-free survival of about 50%.^{16,17} ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine), developed by the Milan group,³ has partial non-crossresistance with MOPP and can cure about 20% of patients not cured with that regimen.¹⁸ ABVD also causes neither sterility nor premature menopause and is less leukemogenic.^{19,20} Hybrid or alternating combinations of MOPP and ABVD cure approximately 10% to 15% more patients than MOPP;^{4,21} however, as shown in a landmark randomized trial by the Cancer and Leukemia Group B (CALGB), both ABVD and MOPP/ABVD are equivalently superior to MOPP in terms of progression-free survival.⁴ These results were confirmed in a large intergroup study in which the MOPP/ABV hybrid regimen was tested against ABVD.⁵ This trial enrolled 856 patients and found no differences in complete response rate, freedom-from-treatment failure or overall survival. By the late 1990s clinical trials had established that ABVD best combines of high efficacy and reduced toxicity and is the standard of care for advanced-stage Hodgkin lymphoma.

The usefulness of irradiation in the treatment of limited-stage Hodgkin lymphoma led to it being tested in a variety of treatment programs for patients with advanced disease. Loeffler and colleagues performed a meta-analysis examining the results from 14 randomized controlled clinical trials including 1740 patients comparing chemotherapy alone with combined modality treatment.²² Although radiotherapy resulted in a significantly improved tumor control rate after 10 years, overall survival was not improved. Worryingly, significantly more deaths unrelated to Hodgkin lymphoma were observed in patients who had been given combined modality treatment with chemotherapy and radiotherapy. Three subsequently reported randomized trials examined the usefulness of radiation for patients in complete remission after chemotherapy for advanced-stage Hodgkin lymphoma and found no significant impact.²³⁻²⁵ Although one study of similar design showed contradictory results, it primarily focused on pediatric patients and patients with limited-stage disease.²⁶ Overall, the negative long-term effects of radiation appear to outweigh any benefits for the usual patient with ad-

vanced-stage disease. Whether there is a role for localized irradiation for patients who start with bulky disease remains to be determined, although it is still often added to the chemotherapy based on intuitive appeal.

Two new regimens have emerged as potentially superior to ABVD. In the Stanford V regimen the drugs are administered weekly for 12 weeks followed by irradiation with 36 Gy to sites of initial tumor bulk (≥ 5 cm).²⁷⁻²⁹ In the most recent update of the mature results from the pilot studies of Stanford V, with a median follow-up of 6.9 years, the actuarial 8-year freedom from progression was 91% and the overall survival was 95%.²⁹ The definitive randomized trial comparing Stanford V + RT with standard ABVD is ongoing. An Italian trial investigating a variation of Stanford V + RT has been conducted but tested a sufficiently different treatment strategy that it can not be used to evaluate the relative efficacy of this regimen.³⁰

The GHSG has tested BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone and procarbazine), a dose-escalated and accelerated combined modality program, plus radiation.^{31,32} The HD9 randomized trial compared COPP/ABVD + RT with standard dose BEACOPP + RT and escalated dose BEACOPP + RT. Irradiation was given to approximately 70% of patients on all three arms based on presence of initial moderately bulky (> 5 cm) or residual nodal abnormalities. The most recent analysis, also with a median follow-up of 6.9 years, included 1195 evaluable patients and demonstrated superior freedom from treatment failure and overall survival for the patients treated with escalated dose BEACOPP + RT (Table 5).^{31,32} Escalated BEACOPP showed a higher but manageable rate of hematologic toxicity. Longer follow-up will be required to determine the true usefulness of escalated BEACOPP + RT. Whether the increased toxicity of this regimen (3% treatment induced mortality, 100% infertility in men, 100% infertility plus premature menopause in most women over the age of 25, increased risk of second neoplasms) can be justified remains to be determined. Of particular note is the fact that the increased efficacy of escalated BEACOPP only translated into a survival benefit in the 20% of patients with the poorest prognosis at diagnosis. The other 80% of patients with advanced Hodgkin lymphoma had the same overall survival whether initially treated with ABVD or escalated BEACOPP because of the availability of effective secondary treatment with high-dose chemotherapy and stem cell transplantation (Table 5).

Translation into Practice

A straightforward plan of treatment for adult patients with Hodgkin lymphoma can be based on clinical stage, presence of B symptoms, International Prognostic Factor Project score and bulkiness of the largest tumor mass (Table 6). It is instructive to examine the implications of applying this approach to regular oncologic practice. Table 7 contains short clinical histories with several typical presentations of Hodgkin lymphoma, the expected results with current

best treatment and the major long-term toxicities for each. The first two cases are representative typical patients with advanced-stage lymphoma at presentation. Initial treatment with ABVD best balances high effectiveness and minimization of potential long-term toxicity conferring a 70% to 80% likelihood of cure; leaving the option of high-dose chemotherapy and autologous stem cell transplantation if disease recurs; preserving fertility and normal ovarian function; and minimizing risk of second neoplasms by avoiding radiation and alkylating agent chemotherapy. The third case describes the rarer presentation of advanced disease with many indicators of poor prognosis. In this situation current best evidence predicts a better survival if intensified chemotherapy is chosen as the first treatment rather than standard ABVD. The best option for a patient such as this is enrollment in a prospective clinical trial such as is being coordinated by ECOG in the United States or the EORTC in Europe and Canada. If that is unavailable and the patient is under the age of 60 years, intensified treatment should be considered employing escalated BEACOPP plus radiation. Finally, the fourth case is one of limited-stage Hodgkin lymphoma. In this situation, with cure highly likely using any of several approaches, the clinician must carefully craft a treatment plan that minimizes late toxicity. A brief course of chemotherapy alone, ABVD for 4 cycles, should be planned and will suffice for most patients, conferring a chance of cure exceeding 90% for those with a complete response after 2 cycles. For the minority with less than a complete response after 2 cycles, switching to involved field radiation permits preservation of that high likelihood of cure with an only modest, but now justified,

Table 5. Results of treatment of advanced stage Hodgkin lymphoma with standard or escalated BEACOPP + RT: the German Hodgkin Study Group (GHSG) trial HD9.

	COPP/ ABVD + RT (A)	BEACOPP std esc + RT (B)	BEACOPP + RT (C)	<i>p</i> (A vs C)
<i>n</i>	260	469	466	
CR %	84	88	96	
5 y FFTF %	67	75	85	< 0.001
5 y OS %	79	84	90	0.004
5 y OS %				
IPFP 0,1	91	91	95	NS
IPFP 2,3	81	90	90	NS
IPFP 4-7	57	85	77	< 0.0099
AML/myelodys (n,%)	1 (0.3)	5 (1.0)	11 (2.3)	

Abbreviations: std, standard; esc, escalated; CR, complete response; FFTF, freedom from treatment failure; IPFP, International Prognostic Factors Project score; NS, not significant; AML/myelodys, acute myelogenous leukemia or myelodysplasia; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone and procarbazine; RT, radiation therapy.

Table 6. Overall approach to primary treatment of Hodgkin lymphoma,

Stage	Bulk [‡]	IPFP score	Treatment
IA, IIA	Low	Not applicable	ABVD x 4 or ABVD x 2 + IFRT*
Any stage with B symptoms or III or IV	Low	0-3	ABVD until 2 cycles past CR (min 6, max 8)
Any stage with B symptoms or III or IV	Low	4-7	Intensified chemotherapy**
Any stage	High	0-7	Chemotherapy as above followed by IFRT to the bulky site

[‡] Bulk, low < 10 cm, high ≥ 10 cm largest diameter of any single mass

* ABVD x 4 if CR after 2 cycles, ABVD x 2 + IFRT if < CR after 2 cycles

**Escalated BEACOPP if IPFP score 4-7 and age less than 60 years

Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine and dacarbazine; CR, complete response; IFRT, involved field radiotherapy; min, minimum; max, maximum.

Table 7. Optimal treatment for various presentations of Hodgkin lymphoma.

Presentation	Hgb g/L	Lymphs x 10 ⁹ /L	Histology	Treatment	Comments
	WBC x 10 ⁹ /L	Alb g/L	IPFP score	Prognosis	
23-year-old man left neck, asymptomatic, mediastinal and retroperitoneal nodes 3-4 cm	134	1.8	Nodular sclerosing	ABVD x 6	Stage III A low bulk; good prognosis; no advantage to highly toxic treatment
	11.2	42	1 (male)	PFS = 80% OS = 90% fertility preserved; cardio/2nd ca risks very low	
46-year-old woman, lumbar pain, night sweats, retroperitoneal and pelvic nodes 3-7 cm, multiple sclerotic lesions lumbar spine + pelvis	107	0.9	Mixed cellularity	ABVD x 6-8	Stage IV _{bone} B intermediate prognosis; no advantage to highly toxic treatment
	8.7	36	3 (age, stage, albumin)	PFS = 75% OS = 85%-90% modestly premature menopause likely; cardio/2nd ca risks very low	
57-year-old man, lumbar pain, night sweats, mediastinal and retroperitoneal nodes 4-6 cm, multiple splenic nodules, marrow positive	99	0.4	Mixed cellularity	Escalated BEACOPP x 6-8	Stage IV _{marrow} B poor prognosis; highly toxic treatment justified but will carry risk of 4%-5 % lethal toxicity
	7.9	32	6 (age, male, stage, Hgb, lymphocytes, albumin)	PFS = 70% OS = 75%-80% sterility; cardio/2nd ca risks substantially increased	
19-year-old woman, asymptomatic, right neck and mediastinal nodes 3-5 cm	132	1.0	Nodular sclerosing	ABVD x 4	Stage II A excellent prognosis; no need for radiation if CR reached after 2 cycles of ABVD
	14.2	44	Not Applicable	PFS = 95% OS = 99% fertility preserved; cardio/2nd ca risks very low	

Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine and dacarbazine; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone and procarbazine; IPFP, International Prognostic Factors Project; cardio, cardiovascular; 2nd ca, second cancer; PFS, progression-free survival; OS, overall survival.

increase in late risk of cardiovascular disease or second malignancy.

Clinicians guiding treatment of Hodgkin lymphoma must proceed with two goals: first, to maximize likelihood of cure; second, to minimize major late toxicity. We must recognize the tension between these goals and strike the

best balance possible. Fortunately, currently available therapies including multi-agent chemotherapy, judicious but limited application of radiation and intensified treatments at diagnosis for carefully selected patients allow us to offer the large majority of patients complication-free long term survival.

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