Published in final edited form as:
Cancer J. 2009 ; 15(2): 150–154. doi:10.1097/PPO.0b013e3181a27018.

The Role of Chemotherapy in Hodgkin's Lymphoma

Pamela Seam, M.D.,
Oncology Fellow, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda MD 20892

John E. Janik, M.D.,
Co-Director, Clinical Trials Team, Metabolism Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda MD 20892

Dan L. Longo, M.D., and
Scientific Director, National Institute on Aging, National Institutes of Health, Baltimore MD 21224

Vincent T. DeVita Jr., M.D.
Amy and Joseph Perella Professor, Yale Cancer Center, New Haven CT 06519

Abstract

The development of curative chemotherapy regimens for the treatment of Hodgkin's lymphoma is one of the true success stories in oncology. Most patients diagnosed with Hodgkin's lymphoma today can be cured. The major task remaining before us is curing as many patients as possible with their initial therapeutic approach while minimizing the acute toxicities and limiting the lifetime risks of important secondary events such as cardiovascular complications and secondary malignancies. In the 40 years since DeVita and colleagues developed the MOPP (Mechlorethamine, Vincristine, Procarbazine, Prednisone) chemotherapy regimen, we have learned a great deal about risk stratification to minimize treatment-related toxicity. Positron-emission tomography may further assist us in reducing radiation treatment without compromising cures. This review will discuss the development of the chemotherapy regimens used in the management of early and advanced stage Hodgkin's lymphoma and the advantages and disadvantages of their use in combination with radiation therapy.

Keywords

Hodgkin's lymphoma; Antineoplastic Agents; Combined Modality Therapy; Positron-Emission Tomography

Introduction

There are few success stories in oncology as rewarding or remarkable as the development of curative therapies for Hodgkin's lymphoma (HL). In 1832, in an article entitled "Some Morbid Appearances of the Absorbent Glands and Spleen," Thomas Hodgkin first characterized the lymphadenopathy and splenomegaly associated with HL [1]. Extended-field radiotherapy became the mainstay of curative therapy until the 1960's when systemic chemotherapy was incorporated into the treatment paradigm to manage disseminated disease. In this paper, we will define the relevant features of the staging system in HL, review the landmark chemotherapeutic regimens used to treat both limited and advanced stage classical HL, and

Corresponding author: John E. Janik, M.D., Building 10CRC, Room 4-5330, 9000 Rockville Pike, Bethesda, MD 20892-1457, janikj@mail.nih.gov, Phone: (301) 402-2913, Fax: (301) 402-1001.

finally, discuss the role of 18-fluorodeoxyglucose positron-emission tomography (^{18}F-FDG-PET) scans in assessing response and minimizing the risk of long-term toxicities. Nodular lymphocyte-predominant Hodgkin's lymphoma (NLPHL), regarded as a separate entity under the WHO lymphoma classification, will not be discussed here.

Staging and Prognostic Evaluation

The Ann Arbor classification defines four clinical and pathologic stages of HL [2]. In 1990, the suffix "X" was incorporated into the classification and indicated the presence of bulky disease, i.e. a single mass exceeding 10 cm in largest diameter or a mediastinal mass exceeding one third of the maximum transverse transthoracic diameter on a standard posterior-anterior chest radiograph at the level of T5–T6 [3]. In North America, the division of HL into limited stage (stage I–IIA with no areas of bulk) and advanced stage (stage III–IV or stage I- II with B symptoms or areas of bulk) has guided modern treatment strategies. The National Cancer Institute of Canada/Eastern Cooperative Oncology Group (NCIC/ECOG) further distinguishes unfavorable early stage patients as those age ≥40, ESR ≥50, mixed cellularity or lymphocyte depleted histology, or ≥4 sites of disease [4]. The therapeutic implications of these and similar subdivisions used by the European cooperative groups remain unclear [5,6].

Limited Stage Disease

Given that HL is a radiosensitive disease, extended-field radiation therapy was the treatment of choice until the late 1980s. Staging laparotomy was frequently performed to confirm that disease was indeed localized. A number of studies demonstrated equivalent or superior long-term disease control in patients receiving chemotherapy alone or combined modality therapy (CMT) versus treatment with radiation therapy alone [5,7–12]. Meta-analyses have solidified these conclusions [11,12].

Specht et al conducted a meta-analysis in which individual patient data were collected on 1688 patients in 13 studies between 1967 and 1988 using mechlorethamine, vincristine sulfate, procarbazine, and prednisone (MOPP) or a MOPP-like regimen with radiation therapy versus radiation therapy alone [11]. The addition of chemotherapy to radiotherapy halved the 10-year risk of treatment failure (15.8% vs 32.7%, $p < 0.00007$), but the effect on overall survival (OS) was not statistically significant. Another analysis of 14 randomized trials performed between 1974 and 1988 and enrolling 1740 patients compared chemotherapy alone with CMT [12]. Among trials in which radiation was added to chemotherapy, the 10-year tumor control rate improved by 11% ($p = 0.0001$) with no improvement in OS ($p = .57$). When additional chemotherapy was substituted for radiation in CMT, no difference in tumor control rates ($p = .43$) was observed although OS significantly improved for the chemotherapy alone group ($p = .045$). The lack of an OS benefit in patients receiving CMT in both metanalyses highlights the impact of radiation-induced cardiovascular complications and secondary neoplasia.

CMT does produce a superior outcome to radiation therapy alone. A phase III intergroup prospective randomized trial of subtotal lymphoid irradiation (SLI) versus doxorubicin, vinblastine, and SLI for stage IA–IIA disease reported a markedly superior failure-free survival (FFS) rate for patients on the CMT arm (94%) compared with the SLI arm (81%) [10]. In another study of stage IA–IIA patients, the freedom from treatment failure (FFTF) at seven years (88%) was significantly better for the 316 patients who received 2 cycles of ABVD plus extended-field radiotherapy (EF-RT) versus the 311 patients who received EF-RT alone (67%) [9].

Ferme et al stratified 1538 patients with untreated stage I–II supradiaphragmatic HL into a favorable prognosis group (n= 542) and an unfavorable prognosis group (n=996) [5,8]. Favorable prognosis patients were randomly assigned to receive 3 cycles of MOPP-ABV plus

involved-field radiotherapy (MOPP-doxorubicin, bleomycin, and vinblastine plus IF-RT) or subtotal nodal radiotherapy. Patients with an unfavorable prognosis were randomly assigned to receive 6 or 4 cycles of MOPP-ABV plus IF-RT or 4 cycles of MOPP-ABV plus subtotal nodal radiotherapy. With 92 months of median follow-up, among patients with a favorable prognosis, the 5-year event-free survival (EFS) rate and 10 year OS estimate were 98% and 97%, respectively, for the CMT group and 92% and 74%, respectively, for the radiotherapy alone group. There was no difference in 5-year EFS rates and 10-year OS estimates among the three treatment groups in patients with an unfavorable prognosis. The authors concluded that early stage favorable patients should receive chemotherapy plus IF-RT whereas unfavorable disease patients should receive four courses of a doxorubicin containing regimen plus IF-RT. This conclusion ignores the possibility that the outcome might be similar or even improved with the use of chemotherapy alone.

Clinical investigations turned to reducing the size of the radiation field, reducing the radiation dose, limiting the number of cycles of chemotherapy, and using chemotherapy alone. We will focus on the latter two approaches, with an emphasis on doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) and ABVD-like regimens which are currently the standard of care for stage I–II HL in the United States [4,7,13–15].

In a phase III trial of 1370 patients with stage I–II favorable disease, Diehl et al randomly assigned patients to 2 or 4 cycles of ABVD followed by IFRT at either 20 Gy or 30 Gy [13]. The reported FFTF after a median observation time of two years was 96.6% with no statistical differences between arms that differed in the number of cycles of chemotherapy or the dose of IF-RT.

In a series of 251 Indian patients, 179 achieved a complete remission (CR) after six cycles of ABVD and were further randomized to IF-RT or no further therapy[14]. The 8-year EFS and OS in the chemotherapy-alone arm were 76% and 89%, respectively, as compared with 88% and 100%, respectively, in the chemotherapy plus IF-RT arm (Laskar S, JCO 2004). The inclusion of pediatric patients and patients with various stages of disease may have affected the results. Notably, among 99 patients with stage I–II disease, there was no difference in EFS or OS between the two arms of the study.

In a study from the Memorial Sloan-Kettering Cancer Center, 152 untreated HL patients with clinical stages IA–IIA, IB–IIB, and IIIA without bulky disease were randomly assigned to 6 cycles of ABVD alone or 6 cycles of ABVD followed by radiation therapy [15]. At 60 months, the freedom from progression (FFP) was 86 % for the ABVD plus radiation therapy arm and 81% (p=0.61) for the ABVD arm alone, while OS for the two arms was 97% and 90%, respectively (p=0.08). The small sample size and the inclusion of patients with B symptoms and IIIA disease may have confounded the results, but they suggest that chemotherapy alone is an acceptable approach for most patients.

Meyer et al conducted a multicenter randomized controlled trial in which 399 patients with nonbulky clinical stage I–IIA HL were stratified into favorable and unfavorable risk cohorts [4]. Patients were randomly assigned to receive either radiotherapy (subtotal nodal radiation for favorable risk or 2 cycles of ABVD followed by subtotal nodal radiation for unfavorable risk) or ABVD as a single modality (4 vs 6 cycles of ABVD based on radiographic response on CT after 2 cycles of chemotherapy). At a median followup of 4.2 years, there was no difference in OS (94 vs 96%, p=0.4) or EFS (88 vs 86%, p=0.06) in patients allocated to CMT versus patients allocated to chemotherapy alone. Although the 5 year freedom from disease progression was superior in patients who received radiation therapy (p=0.006), there was a trend toward an increased number of deaths due to second cancers and cardiovascular events. The survival of relapsed patients on both arms of the study was over 70%.

The National Cancer Institute (NCI) reported 25 year followup on 136 patients randomized to receive radiation therapy or MOPP chemotherapy [16]. Disease-free survival (DFS) was 61% and 87% for radiation and MOPP, respectively (p=0.0034). OS was 63% and 81% for radiation and MOPP, respectively (p=0.048). Among the patients who remained in CR from chemotherapy, 25-year OS was 93% versus 78% for patients treated with radiation therapy (p=0.05). Secondary malignancies and heart disease accounted for excess deaths among patients in CR previously treated with mantle field radiation therapy. Based on these results and the curative potential of chemotherapy alone in the majority of patients, radiation should be reserved for the 5–7% of patients whose disease does not respond to chemotherapy.

Advanced Stage Disease

In 1963, the NCI initiated a pilot study to test MOPP chemotherapy in 43 patients with advanced HL [17]. MOPP was the first regimen capable of prolonging DFS in advanced disease and the first such success in any disseminated solid tumor [18]. Providing the same therapeutic benefit as MOPP with less hematologic toxicity and lower rates of infertility, ABVD eventually replaced MOPP as the standard of care for advanced HL in the United States [19]. Various combinations of MOPP and ABVD were tested over the next twenty years, but none proved better than ABVD alone. In phase I–II studies, Stanford V (doxorubicin, vinblastine, mechlorethamine, etoposide, vincristine, bleomycin, and prednisone) and BEACOPP (bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, and prednisone), both administered with radiation therapy, also demonstrated clinical efficacy [20–22]. Phase III trials comparing each of them to ABVD are ongoing.

DeVita et al first reported that MOPP achieved high CR rates (81%), durable complete remissions (29–42 months), and long-term DFS (47% DFS at 4 years) in stage III–IV patients [23]. At 14 years of followup, 157 of 188 treated patients (84%) entered a CR with 101 patients (66%) remaining disease free more than 10 years from the end of treatment [18].

MOPP, however, caused reversible bone marrow depression, neurotoxicity, and permanent azoospermia in nearly 100% of men [18,24]. Whereas most women age ≤ 26 years regained normal menses following cessation of therapy, 41% of women age ≥ 26 became amenorrheic. Nearly all women experienced premature menopause typically in their late 30s. Only one patient in the NCI series developed acute leukemia, but acute leukemia and myelodysplastic syndrome (MDS) after MOPP or MOPP in combination with radiotherapywere reported elsewhere [25,26].

To improve treatment outcome, the Milan group developed ABVD "… on an empirical rather than a solid scientific basis…" [19,27]. Less toxic than MOPP, ABVD became the standard of care in advanced HL. In an equivalence trial, 60 patients with untreated stage IIB–IVB HL were randomly assigned to 6 cycles of ABVD vs 6 cycles of MOPP. MOPP (76%) and ABVD (75%) produced the same number of CRs with bone marrow suppression representing the main dose-limiting factor. Among 232 previously untreated stage IIB, IIIA, and IIIB patients randomly assigned to receive 3 cycles of MOPP or ABVD followed by radiotherapy, the 7-year freedom from progression (80.8% vs 62.8%, p<0.002), relapse-free survival (87.7% vs 77.2%, p=0.06), and OS (77.4% vs 67.9%, p=0.03) were higher for ABVD than MOPP [28]. There were no significant abnormalities in cardiopulmonary function with either regimen.

To maximize the cure rates achieved with MOPP and ABVD, clinical trials incorporated multiple non-cross-resistant agents and then alternated the component drugs (MOPP/ABVD), sequenced them (MOPP → ABVD), or integrated 7 out of 8 drugs into a hybrid therapy (MOPP/ABV) [29–32]. Seventy patients with advanced HL, including 16 in first relapse following radiotherapy, were treated with hybrid MOPP/ABV regimen over 8 months [30]. IF-RT was given to partial responders. The actuarial OS at 49 months for 54 untreated patients was 90%

with no reported drug-induced pulmonary or cardiac toxicity. These results led to a randomized 301 patient study of untreated stage IIIB, IVA, or IVB disease or disease in first relapse after radiotherapy comparing the MOPP/ABV hybrid regimen or MOPP alternating with ABVD [33]. Five year OS rates and 5-year failure-free survival (FFS) rates for the two regimens were similar. The MOPP/ABV regimen (27%) was associated with significantly more episodes of febrile neutropenia and stomatitis vs alternating MOPP/ABVD (10%) ($p = .0001$). Although the MOPP/ABV hybrid was as effective as ABVD in an intergroup trial, the incidence of MDS and acute leukemia dampened support for the regimen [34].

In 1992, Cancer and Leukemia Group B (CALGB) reported a landmark trial comparing MOPP alone for 6–8 cycles, MOPP alternating with ABVD for 12 cycles, and ABVD alone for 6–8 cycles [35]. Lower doses of mechlorethamine and vincristine were used as compared to the original MOPP regimen. In this multicenter study, 361 HL patients with untreated stage III–IV disease or relapsed disease after radiotherapy for localized disease were randomly assigned to receive one of the three regimens. CR rates were 67% for MOPP, 82% for ABVD, and 83% for MOPP-ABVD ($p=0.006$ comparing MOPP with the doxorubicin-containing regimens treatments). At 5 years, FFS rates were 50%, 61%, and 65% for MOPP, ABVD, and MOPP-ABVD, respectively ($p=0.02$ for the comparison of MOPP with the other regimens). There were no differences in OS at 5 years: 66% for MOPP, 73% for ABVD, and 75% for MOPP-ABVD ($p=0.28$ comparing MOPP with the doxorubicin-containing regimens). ABVD therapy was clearly as effective as MOPP alternating with ABVD, and both were superior to MOPP alone. Furthermore, ABVD was less myelotoxic than MOPP with lower rates of severe (18% versus 47–53%) and life-threatening (3% versus 21–28%) neutropenia.

Six percent of patients in the CALGB study did, however, develop severe pulmonary toxicity with three patients dying while on therapy [35]. The Stanford V regimen was therefore developed to maintain or improve the cure rate seen with ABVD or MOPP-like regimens while minimizing acute and long-term toxicities [20]. Administered over 12 weeks, the 7-drug regimen reduced the cumulative doses of bleomycin, doxorubicin, and nitrogen mustard and omitted procarbazine. Although the first 25 patients received 36 to 44 Gy of mantle irradiation for bulky mediastinal disease, nodular spleens, and persistent nodal disease on CT 2 weeks after the completion of chemotherapy, the protocol was modified to give 36 Gy only to sites of disease 5 cm or greater at diagnosis and macroscopic splenic involvement. With a median follow-up 5.4 years, the 5 year FFP was 89% and OS 96% among 142 patients with stage III–IV or locally extensive mediastinal stage I–II HL [21]. There were no secondary leukemias and no observed cardiopulmonary toxicity, though the follow-up period was short.

In the only published comparison of ABVD, Stanford V, and a MOPP-like regimen, Gobbi et al randomized 365 patients with stage IIB, III, or IV HL to receive 6 cycles of ABVD, 3 cycles of Stanford V, or 6 cycles of MOPPEBVCAD (MOPP plus epidoxorubicin, bleomycin, vinblastine, lomustine, doxorubicin, and vindesine) [36]. Among responding patients, 2 sites of previously bulky disease were irradiated 4–6 weeks after the end of chemotherapy. With respect to CR rate, 5 year FFS, and 5 year PFS, Stanford V was inferior to ABVD and MOPPEBVCAD with no significant differences in OS among the three regimens. Response assessment occurred at different times for patients receiving different regimens (8 and 12 weeks for the first and final assessment in Stanford V patients versus 16 and 24 weeks for ABVD and MOPPEBVCAD patients), and this difference may have lead to inferior results for Stanford V. The initiation of radiotherapy 4–6 weeks after the completion of chemotherapy in the Italian study (versus 2 weeks as written in the original Stanford V protocol) may also have played a role. Finally, radiotherapy being limited to two sites of disease in the Stanford V arm and being administered to only 66% of patients in the Italian study (vs 90% of patients in the original Stanford V study) may have influenced the outcome.

In 1991, the German Hodgkin's Lymphoma Group (GHSG) introduced the regimen BEACOPP [22]. The regimen essentially represented a rearrangement of the COPP/ABVD regimen with shorter treatment duration (24 vs 32 weeks) and higher dose intensity than COPP/ABVD with increased doses of doxorubicin and cyclophosphamide. Etoposide was included in the regimen, and IF-RT (30 Gy) was given to all sites of initial bulky disease or to residual tumor remaining after chemotherapy. In the pilot study, 29 untreated patients with stage IIB–IV HL received 8 cycles of BEACOPP [22]. The study was later amended to allow for the inclusion of filgrastim, the restriction of etoposide to the first three days of therapy, and a decrease in the dose of doxorubicin to 25 mg/m2 (from 40 mg/m2). Twenty-one patients (72%) received consolidating radiotherapy. At a median follow-up of 40 months, the freedom from treatment failure (FFTF) rate was 89%. Toxicities were tolerable with grade III/IV neutropenia occurring in 28% of chemotherapy cycles with no treatment-related deaths.

Escalated BEACOPP increased the doses of doxorubicin (from 25 mg/m2 to 35 mg/m2), cyclophosphamide (from 650 mg/m2 to 1200 mg/m2), and etoposide (from 100 mg/m2 to 200 mg/m2) [37]. Filgrastim was given to prevent prolonged neutropenia and severe infections. Among 60 stage IIB–IVA patients, the FFTF rate was 90% at 32 months. Seventy-three percent of these patients received radiotherapy to initial bulk lesions and residual disease in addition to 8 cycles of chemotherapy. Although between 71% and 76% of patients developed grade III/IV neutropenia, there was no corresponding rate of grade III/IV infections. Four patients developed secondary malignancies, including two leukemias 28 and 35 months after the completion of therapy.

In a prospective study, the GHSG randomly assigned 1201 patients with unfavorable stage IIB, IIIA–IIIB, or IV to receive 8 cycles of COPP-ABVD, BEACOPP, or increased dose BEACOPP, each followed by radiotherapy (30 Gy to sites of initial bulky disease and 40 Gy to any residual tumor) [38]. Approximately 70% of patients on all three arms received irradiation. The study was terminated at the first interim analysis when it was determined that both BEACOPP groups were superior to COPP-ABVD in terms of the rate of FFTF. The 5-year rate of FFTF was 69% in the COPP-ABVD arm, 76% in the BEACOPP arm, and 87% in the increased-dose BEACOPP arm. Five-year rates of OS were not significantly different between standard dose BEACOPP and escalated dose BEACOPP. There was, however, a statistically significant difference in OS (p=0.002) between the COPP-ABVD group (83%) versus the escalated BEACOPP group (91%). The improvement in FFTF and OS in the escalated BEACOPP group was accompanied by an increased incidence of acute hematologic effects. Ninety percent of patients developed grade 4 neutropenia and 22% patients developed grade 3 or 4 infections. Twenty-two patients developed secondary neoplasms with 14 developing acute leukemias. Thirteen of these patients were in the BEACOPP groups versus one in the COPP-ABVD group. Ten and 9 patients developed solid tumors and second non-Hodgkin's lymphomas (NHL), respectively, in the BEACOPP groups. Three and 7 patients developed solid tumors and second NHLs, respectively, in the COPP-ABVD group.

Whether the same improvement in FFTF and OS would have been seen if patients had been randomly assigned to ABVD instead of ABVD-COPP remains unclear [38]. Several factors have prevented the German regimen from gaining acceptance around the world: no data from a randomized phase III trial demonstrate the superiority of BEACOPP over ABVD; BEACOPP is associated with an increased incidence of acute and late toxicities; and the inclusion of radiation therapy in the treatment of patients with advanced disease increases the risks of second cancers and potentially fatal premature heart disease.

The Role of FDG-PET scans in the Management of Both Limited and Advanced Stage Disease

Even as the cure rate for advanced HL approaches 80%, a major concern remains late-onset toxicities including the risk of second malignancies and an increased risk of myocardial infarction or stroke in patients who receive mediastinal radiotherapy and cervical radiation therapy, respectively. The goal of therapy is to maximize therapeutic benefit while minimizing morbidity and mortality. The most frequently used prognostic model in HL is a 7-factor prognostic scoring system, the International Prognostic Score (IPS), that predicts 5-year rates of FFP [39]. Using data collected from 5141 patients treated with chemotherapy for advanced HL, Hasenclever et al identified seven factors with independent prognostic effects, including albumin < 4g/dL, hemoglobin < 10.5 g/dL, male sex, age > 45 years, stage IV disease, white blood cell count >15000/mm3, and lymphocyte count <600/mm3. Bcause the IPS relies on fixed pretreatment variables, it neglects possibly the most important prognostic factor, the chemosensitivity of the tumor. Distinguishing between metabolically active lymphoma and residual scar tissue, 18F-FDG-PET may play an important role in the development of a patient response-based treatment strategy.

Hutchings et al prospectively examined the prognostic value of interim FDG-PET after 2 cycles of chemotherapy in patients with all stages of HL [40]. Among 16 patients with positive PET scans, 11 patients progressed, and 2 of these patients died. Among 61 patients with negative PET scans, 58 patients were alive and free of disease at a median followup of 23 months. The two-year progression free survival (PFS) for PET-positive and PET-negative patients was 96% and 0%, respectively, and in multivariate regression analyses, PET results after 2 cycles of therapy were shown to be a stronger predictor of PFS than clinical stage or extranodal disease.

Gallamini et al further demonstrated the superior prognostic value of midtreatment FDG-PET scans over the IPS [39,41]. Among 260 patients with newly diagnosed advanced HL who underwent FDG-PET scans after completing 2 cycles of ABVD, the 2 year PFS for patients with positive PET scans was 12.8%. For patients with negative midtreatment PET results, the 2 year PFS was 95%. A multivariate regression analysis was performed and included both the IPS (as a continuous variable) and PET results after 2 cycles of chemotherapy. Only the PET results and stage IV disease had independent prognostic value. The question of whether the midtreatment PET scan should be performed after 2 or after 3 cycles of therapy remains unanswered.

There is only one report in the literature that implements a risk-adapted approach to treating HL [42]. In this study, 108 patients with newly diagnosed HL and adverse prognostic factors received therapy first based on their IPS score and then based on their midtreatment FDG-PET or gallium scan [39]. Patients with an IPS ≤ 2 received 2 cycles of standard BEACOPP while patients with an IPS ≥ 3 received 2 cycles of escalated BEACOPP. Patients with a positive interim scan then received 4 cycles of escalated BEACOPP while patients with a negative interim scan received 4 cycles of standard BEACOPP. Among 69 patients with early unfavorable or standard risk disease, 58 received 6 cycles of standard BEACOPP and 10 received 2 cycles of standard BEACOPP followed by 4 cycles of escalated BEACOPP. With a median followup of 46 months, the 5-year EFS and OS rates for this group were 84% and 90%, respectively. Among 39 high-risk patients, 31 received 2 cycles of escalated BEACOPP followed by 4 cycles of standard BEACOPP. Only 7 patients received 6 cycles of escalated BEACOPP. With a median followup of 49 months, the 5-year EFS and OS rates for this group were 85% and 91%, respectively. The similar EFS and OS rates observed in both risk groups suggest that a risk-adapted treatment plan may be reasonable. To confirm the benefit of more intensive therapy in the setting of a positive midtreatment PET scan, larger prospective clinical trials are needed.

Conclusion

The curative potential of combined chemotherapy was first realized with the introduction of MOPP in the 1960s. ABVD has maintained the high response rate seen with MOPP, minimized some of its toxicities, and substituted others. Because randomized clinical trial data have never proven that CMT is superior to chemotherapy alone, the widespread use of radiation therapy in all stages of disease seems unjustified. As early and late toxicities associated with the use of radiation therapy affect an increasing fraction of long-term survivors, the curative potential of clinical staging and six cycles of chemotherapy needs to be reexamined. Future clinical investigations should focus on integrating functional imaging with FDG-PET scans into the treatment paradigm as a decision-making tool to identify the small percentage of patients who require more intensive therapy to increase the likelihood of cure.

Acknowledgments

Supported in part by the Intramural Research Program of the National Cancer Institute, National Institutes of Health.

References

1. Abbondanzo SL. Thomas Hodgkin. Ann Diagn Pathol 2003;7(5):333–4. [PubMed: 14571438]
2. Carbone PP, et al. Report of the Committee on Hodgkin's Disease Staging Classification. Cancer Res 1971;31(11):1860–1. [PubMed: 5121694]
3. Lister TA, 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(11):1630–6. [PubMed: 2809679]
4. Meyer RM, 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 (21):4634–42. [PubMed: 15837968]
5. Noordijk EM, 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 Cancer H7 randomized controlled trials. J Clin Oncol 2006;24(19):3128–35. [PubMed: 16754934]
6. Duhmke E, et al. Low-dose radiation is sufficient for the noninvolved extended-field treatment in favorable early-stage Hodgkin's disease: long-term results of a randomized trial of radiotherapy alone. J Clin Oncol 2001;19(11):2905–14. [PubMed: 11387364]
7. Longo DL, et al. Radiation therapy versus combination chemotherapy in the treatment of early-stage Hodgkin's disease: seven-year results of a prospective randomized trial. J Clin Oncol 1991;9(6):906–17. [PubMed: 2033427]
8. Ferme C, et al. Chemotherapy plus involved-field radiation in early-stage Hodgkin's disease. N Engl J Med 2007;357(19):1916–27. [PubMed: 17989384]
9. Engert A, 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(23):3495–502. [PubMed: 17606976]
10. Press OW, 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(22):4238–44. [PubMed: 11709567]
11. Specht L, et al. 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. International Hodgkin's Disease Collaborative Group. J Clin Oncol 1998;16(3):830–43. [PubMed: 9508163]
12. Loeffler M, 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(3):818–29. [PubMed: 9508162]

13. Diehl V. HD10: Investigating reduction of combined modality treatment intensity in early stage Hodgkin's lymphoma. Interim analysis of a randomized trial of the German Hodgkin Study Group (GHSG) Journal of Clinical Oncology 2005;23(16S)
14. Laskar S, et al. Consolidation radiation after complete remission in Hodgkin's disease following six cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine chemotherapy: is there a need? J Clin Oncol 2004;22(1):62–8. [PubMed: 14657226]
15. Straus DJ, 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(12):3483–9. [PubMed: 15315964]
16. Longo D, et al. A Prospective Trial of Radiation Alone vs Combination Chemotherapy Alone for Early-Stage Hodgkin's Disease: Implications of 25-Year Follow-Up to Current Combined Modality Therapy. Blood 2006;108:98.
17. DeVita VT Jr, Carbone PP. Treatment of Hodgkin's disease. Med Ann Dist Columbia 1967;36(4): 232–4. passim. [PubMed: 5232852]
18. Longo DL, et al. Twenty years of MOPP therapy for Hodgkin's disease. J Clin Oncol 1986;4(9): 1295–306. [PubMed: 3528400]
19. Bonadonna G, et al. Combination chemotherapy of Hodgkin's disease with adriamycin, bleomycin, vinblastine, and imidazole carboxamide versus MOPP. Cancer 1975;36(1):252–9. [PubMed: 54209]
20. Bartlett NL, et al. Brief chemotherapy, Stanford V, and adjuvant radiotherapy for bulky or advanced-stage Hodgkin's disease: a preliminary report. J Clin Oncol 1995;13(5):1080–8. [PubMed: 7537796]
21. Horning SJ, et al. Stanford V and radiotherapy for locally extensive and advanced Hodgkin's disease: mature results of a prospective clinical trial. J Clin Oncol 2002;20(3):630–7. [PubMed: 11821442]
22. Diehl V, et al. BEACOPP: an intensified chemotherapy regimen in advanced Hodgkin's disease. The German Hodgkin's Lymphoma Study Group. Ann Oncol 1997;8(2):143–8. [PubMed: 9093722]
23. Devita VT Jr, Serpick AA, Carbone PP. Combination chemotherapy in the treatment of advanced Hodgkin's disease. Ann Intern Med 1970;73(6):881–95. [PubMed: 5525541]
24. Viviani S, et al. Gonadal toxicity after combination chemotherapy for Hodgkin's disease. Comparative results of MOPP vs ABVD. Eur J Cancer Clin Oncol 1985;21(5):601–5. [PubMed: 2408897]
25. Valagussa P, et al. Second acute leukemia and other malignancies following treatment for Hodgkin's disease. J Clin Oncol 1986;4(6):830–7. [PubMed: 3711960]
26. Blayney DW, et al. Decreasing risk of leukemia with prolonged follow-up after chemotherapy and radiotherapy for Hodgkin's disease. N Engl J Med 1987;316(12):710–4. [PubMed: 3821809]
27. Santoro A, Bonfante V, Bonadonna G. Salvage chemotherapy with ABVD in MOPP-resistant Hodgkin's disease. Ann Intern Med 1982;96(2):139–43. [PubMed: 6174060]
28. Santoro A, et al. Long-term results of combined chemotherapy-radiotherapy approach in Hodgkin's disease: superiority of ABVD plus radiotherapy versus MOPP plus radiotherapy. J Clin Oncol 1987;5 (1):27–37. [PubMed: 2433409]
29. Bonadonna G, Valagussa P, Santoro A. Alternating non-cross-resistant combination chemotherapy or MOPP in stage IV Hodgkin's disease. A report of 8-year results. Ann Intern Med 1986;104(6): 739–46. [PubMed: 2422994]
30. Klimo P, Connors JM. MOPP/ABV hybrid program: combination chemotherapy based on early introduction of seven effective drugs for advanced Hodgkin's disease. J Clin Oncol 1985;3(9):1174–82. [PubMed: 2411881]
31. Viviani S, et al. Alternating versus hybrid MOPP and ABVD combinations in advanced Hodgkin's disease: ten-year results. J Clin Oncol 1996;14(5):1421–30. [PubMed: 8622055]
32. Glick JH, et al. MOPP/ABV hybrid chemotherapy for advanced Hodgkin's disease significantly improves failure-free and overall survival: the 8-year results of the intergroup trial. J Clin Oncol 1998;16(1):19–26. [PubMed: 9440718]
33. Connors JM, et al. Treatment of advanced Hodgkin's disease with chemotherapy--comparison of MOPP/ABV hybrid regimen with alternating courses of MOPP and ABVD: a report from the National Cancer Institute of Canada clinical trials group. J Clin Oncol 1997;15(4):1638–45. [PubMed: 9193364]

34. Duggan DB, et al. Randomized comparison of ABVD and MOPP/ABV hybrid for the treatment of advanced Hodgkin's disease: report of an intergroup trial. J Clin Oncol 2003;21(4):607–14. [PubMed: 12586796]
35. Canellos GP, et al. Chemotherapy of advanced Hodgkin's disease with MOPP, ABVD, or MOPP alternating with ABVD. N Engl J Med 1992;327(21):1478–84. [PubMed: 1383821]
36. Gobbi PG, et al. ABVD versus modified stanford V versus MOPPEBVCAD with optional and limited radiotherapy in intermediate- and advanced-stage Hodgkin's lymphoma: final results of a multicenter randomized trial by the Intergruppo Italiano Linfomi. J Clin Oncol 2005;23(36):9198–207. [PubMed: 16172458]
37. Tesch H, et al. Moderate dose escalation for advanced stage Hodgkin's disease using the bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, and prednisone scheme and adjuvant radiotherapy: a study of the German Hodgkin's Lymphoma Study Group. Blood 1998;92 (12):4560–7. [PubMed: 9845521]
38. Diehl V, et al. Standard and increased-dose BEACOPP chemotherapy compared with COPP-ABVD for advanced Hodgkin's disease. N Engl J Med 2003;348(24):2386–95. [PubMed: 12802024]
39. Hasenclever D, Diehl V. A prognostic score for advanced Hodgkin's disease. International Prognostic Factors Project on Advanced Hodgkin's Disease. N Engl J Med 1998;339(21):1506–14. [PubMed: 9819449]
40. Hutchings M, et al. FDG-PET after two cycles of chemotherapy predicts treatment failure and progression-free survival in Hodgkin lymphoma. Blood 2006;107(1):52–9. [PubMed: 16150944]
41. Gallamini A, 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(24):3746–52. [PubMed: 17646666]
42. Dann EJ, 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(3): 905–9. [PubMed: 17018856]