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ABSTRACT: With continued progress and success in clinical care, the management of patients with Hodgkin lymphoma (HL) has undergone continuous revision to improve patient care outcomes and limit acute and late treatment effects on normal tissue imposed by therapy. Hodgkin lymphoma is a disease that affects children, adolescents, and adults. Clinical management strategies are influenced by the patient's age at diagnosis, tumor burden, response to induction therapy, and potential expectation of treatment impact on normal tissue. The approach to patient management varies in many parts of the world and is influenced by treatment availability, physician training, and medical culture. Differences in approach are important to understand for accurately comparing and contrasting outcome studies. In this article, we will identify current areas of common ground and points of separation in patient care management for HL. Opportunities for clinical trial strategies will be defined for future clinical trials.

KEYWORDS: Hodgkin lymphoma, therapy, clinical trial

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Introduction

Decades of successful clinical investigator effort have established modern management strategies for Hodgkin lymphoma (HL) which have led to improved patient outcomes. These risk-adaptive patient care strategies apply chemotherapy and radiation therapy (RT) determined by patient stage, volume of disease, risk of recurrence, response to induction therapy, and evaluation of risk for normal tissue outcome. Based on response to initial chemotherapy, future studies for patients of all age groups will further adapt therapy by adjusting the extent of chemotherapy and the use of RT. Despite the infrequent diagnosis of HL, cooperation between multidisciplinary investigators has led to increased patient enrollment on HL clinical trials in Europe and North America. This is important as the disease has an annual incidence of 2.4 cases per 100 000 people with 0.4 deaths per 100 000 people. In other words, 0.2% of people will develop HL in their lifetime with approximately 85% of all patients surviving 5 years from the initial diagnosis.[1] Participation in clinical trials has served to significantly advance our understanding of treatment and adjust management strategy in this rare and unique disease. Worldwide trials will help answer questions affecting subsets of the HL population in a timely manner.

Over the past several decades, European and North American clinical investigators have conducted multiple successful clinical trials in early-, intermediate-, and advanced-stage HL. As a result of patient participation on protocol, studies are now powered to answer important questions required for the practice of modern clinical oncology. It has been gratifying to recognize the willingness of investigators and patients participating in studies that are designed to answer challenging modern practice questions about the specific and increasingly important subsets of the HL patient population. Worldwide participation will become essential as biomarker development serves to further define the HL patient population subsets. These subsets include younger and older patients at diagnosis and those patients identified with unique evolving clinical features and biomarkers not yet fully characterized. As we personalize and tailor therapy in this rare and age-agnostic disease, we can ask more specific questions and adjust treatment to patient indication and response to induction therapy. Global study participation will be essential to meet more tailored study accrual objectives.

In this article, the current status of HL management in clinical trials will be reviewed and the status of current protocols in Europe and the United States/North America will be discussed. Differences in management practice as well as areas of protocol alignment will be presented. Opportunities and strategies for clinical trial globalization will be explored.

Initial Medical Evaluation

The medical evaluation of patients has become more uniform between European and North American investigators. A medical history, including an evaluation of the presence or absence of B symptoms (constitutional symptoms including fever, night sweats, and weight loss of >10% of total body weight over 6 months), needs to be documented as well as other disease-related symptoms

such as fatigue, pruritus, and alcohol-induced pain. Chest x-ray and computed tomographic (CT) scan of the neck, chest, abdomen, and pelvis are mandatory studies. A baseline positron emission tomography (PET) may also be performed. Many clinical trials require PET scans. Because PET is very sensitive for bone marrow involvement, bone marrow biopsy is no longer uniformly required. If a PET study is not available, bone marrow biopsy is required. A complete blood count, erythrocyte sedimentation rate (ESR), and blood chemistries are required as are screening for hepatitis B and C and human immunodeficiency virus. A thorough cardiopulmonary evaluation is required for patients at risk for acute/long-term complications. Reproductive counseling is important to both sexes. There is no disagreement on these points between European and North American study groups. International collaboration on the evaluation process is feasible as much of the workup is already agreed on by members of the international oncology community.

Staging and Eligibility

Staging has been relatively uniform between groups in Europe and North America. Stage I patients involve one nodal group and stage II patients involve more than one nodal group on the same side of the diaphragm. Stage III patients have nodal disease on both sides of the diaphragm and stage IV patients have parenchymal, bony, or visceral disease as defined on imaging. The A and B categories are also assigned to further describe the disease. Patients assigned as B have constitutional symptoms including fever, night sweats, and weight loss of >10% of total body weight over 6 months. The A category is assigned if the patient has no B symptoms.

To compare treatment strategies between groups, we need to assess and understand the differences in how patients are characterized for favorable/unfavorable early-stage status as well as define intermediate- and advanced-stage status. There are differences between individual European and North American groups. Defining unfavorable status for early-stage patients, the German Hodgkin Study Group (GHSG) and the National Cancer Institute's (NCI) National Clinical Trials Network (NCTN) do not list specific age criteria. Patients ≥50 years of age in the European Organisation for Research and Treatment of Cancer (EORTC) and ≥40 in the National Cancer Institute of Canada (NCIC) Clinical Trials Group are defined as unfavorable. An ESR of >50 for A patients and >30 for B patients for the GHSG and the EORTC and an ESR of 50 or any B symptoms in the NCIC and NCTN define unfavorable status. A mediastinal mass ratio of >0.33 defines unfavorable status for the GHSG and the NCTN. The NCIC defines a ratio of 0.33 or size >10 cm as unfavorable and the EORTC defines a mediastinal mass ratio of 0.35 as unfavorable. Three or more nodal sites for the EORTC, NCIC, and the NCTN and more than 2 sites for the GHSG are assigned to unfavorable status. The GHSG also assigns unfavorable status to patients with any extranodal site of disease. Mixed cellularity and lymphocyte-depleted histology define unfavorable status for the NCIC and any site >10 cm defines unfavorable status for the NCTN. As can be seen, a thorough understanding of the definitions of HL is required to make certain that specific patient groups can be compared in different studies. These differences should be considered relatively modest in nature and with international collaboration; common ground can likely be achieved in establishing worldwide clinical trials. In the National Institutes of Health (NIH) registry of clinical trials (ClinicalTrials.gov), there are more than 200 institutions outside of the United States that participate in clinical trials; therefore, reaching closure on common platforms for analysis this objective is within our grasp.[2]

History of Clinical Trials in HL

Sir Thomas Hodgkin in 1832 is credited with the initial description of HL when he reported on a series of patients with enlarged lymph nodes and splenomegaly which appeared quite different from other known diseases at that time. Toward the end of the 19th century, pathologists working in the United States and Germany (Dorothy Reed and Carl Sternberg) identified many of the classic initial descriptions of the disease, and the recently discovered x-rays were applied to successfully treat enlarged lymph nodes. The introduction of the modern linear accelerator and the development of a 4-drug chemotherapy model at the NCI known as MOPP (mechlorethamine, oncovin, procarbazine, and prednisone) began a series of clinical trial models that led to successful patient treatment programs.[3] The initial programs had protracted therapy following successful first-line therapy models for childhood and adult leukemia. European investigators introduced ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) to attenuate chemotherapy-associated side effects of management and several European groups, including the EORTC and GHSG, began clinical trial investigations. The GHSG introduced a more intensive 7-drug regimen BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) with improved early response rates in patients with advanced disease coupled with more early toxicity and long-term sterility. This resulted in a dual and conflicted approach to modern management. Many European investigators argued for a more aggressive early chemotherapy approach in the management of very high-risk patients to maximize freedom from relapse at the possible expense of acute and long-term toxicity. North American investigators favored a more tailored chemotherapy approach and reserve additional chemotherapy for patients who progressed despite initial management. With improved response rates and cure with chemotherapy, RT has been strategically used in clinical studies. Further improvements in diagnosis, including more precise definition of the tumor tissue, have been recognized with the application of immunologic markers. After more than 100 years of investigative science, investigators have confirmed the B-cell origin of HL. These efforts have been promoted by single investigators and

clinical group processes covalidated by collaborative investigation and clinical trials worldwide.

Although many process improvements are provided by individual investigators, anatomic and metabolic diagnostic imaging tools, immunopathology, enhanced disease characterization, and improved therapy technology, meaningful progress in strategic clinical management has been made by participation in clinical group protocol activity. Moving forward, cooperative multigroup protocols will be required to answer important questions including patient-specific tumor control and normal tissue outcome. In this effort, investigators set aside personal practice preferences and commit to common protocols to answer important clinical trial questions. Given the rare occurrence of the disease, management issues, including duration and intensity of therapy, can be addressed and long-term outcome questions can be answered. Both the European Union and the United States/North America groups have had significant success in conducting HL clinical trials which reflects the changes in strategy for patient care.[4]

HL Clinical Trials: United States and North America

Early cooperative group HL studies largely centered in the pediatric groups permitted adolescent and young adult participation. Often these studies treated patients with extended cycles of chemotherapy and large-volume RT reflecting the enthusiasm of initiating and maintaining response to therapy. Investigators were less cognizant of the effects of management on normal tissue and priority was placed on tumor control. In this era, more therapy was considered more optimal than less therapy. The Pediatric Oncology Group (POG) protocol 8725 evaluated what would be called today, intermediate-, early-, and advanced-stage patients with HL. Patients were treated with 8 cycles of hybrid MOPP-ABVD chemotherapy. Following completion of chemotherapy, the patients were randomized to receive RT to sites of disease defined on imaging at presentation or observed. Radiation right-left lateral volume attenuation was permitted in the mediastinum to limit dose to pulmonary parenchyma, whereas all sites of disease at presentation required postchemotherapy RT. At 5 years, there was no apparent added benefit to the addition of RT.[5] However, more than 30% of patients treated with RT on study had volume deviations, specifically indicating that not all areas of disease at presentation were treated per study guidelines or included in the treatment fields. If those patients receiving RT per protocol were compared with patients receiving chemotherapy alone, the survival of those treated with RT was improved by 10% which was statistically significant (Table 1).[6] This indicated that RT plays an additive role to chemotherapy but only when applied using a uniform standard. As the additive benefit was 10%, this also implied that a large number of patients were successfully treated with chemotherapy alone. If the patients who would not perform well with chemotherapy alone could be identified, then selected patients could be treated with RT. Further review of the 8725 data found that when RT was applied not in accordance with protocol guidelines, there appeared to be no added benefit to patients treated with 8 cycles of hybrid chemotherapy. It is important to acknowledge this point when we establish an argument supporting the use of modern RT in this disease. This study opened the question of evaluating the role of real-time interventional quality assurance in RT to improve protocol compliance and strengthen study analysis. Deviation rates of 30% would not permit important study questions to be answered in a rare disease and efforts were made to address this issue as part of cooperative group study participation.

Table 1. Pediatric Oncology Group protocol 8725 survival according to treatment.[a]

TREATMENT	5-Y RELAPSE-FREE SURVIVAL, %
Arm 1: chemotherapy alone	85
Arm 2: chemotherapy + radiation therapy	
Appropriate volume	96
Major and minor deviations	86

Relapse-free survival indicating significantly better results when the radiation therapy was in accordance with protocol specifications.
[a]Only patients who were in complete remission at the end of chemotherapy.

This study led to a series of risk-adapted protocols evaluating reduction in therapy in early- and intermediate-stage patients. Children's Oncology Group (COG)/POG protocol 9426 evaluated the role of response-adapted chemotherapy in early-stage patients with only 2 cycles of doxorubicin, bleomycin, vincristine, and etoposide chemotherapy given to patients who achieved a rapid early response (RER) using anatomical and metabolic (gallium) imaging followed by 25.5 Gy to sites of original involvement with disease. Patients deemed slow early responders (SERs) received an additional 2 cycles of chemotherapy followed by 25.5 Gy. Real-time central review was used to ensure compliance. The study demonstrated no difference in survival between the groups suggesting that reduced therapy can be selectively applied to early-stage patients with favorable response to initial chemotherapy. The COG protocol 9425 evaluated ABVE-PC (doxorubicin, bleomycin, vincristine, etoposide, prednisone, and cyclophosphamide) for 3 or 5 cycles based on initial response to chemotherapy with 21 Gy delivered to all sites of disease at presentation in patients with intermediate risk factors. Highly favorable outcomes were seen in both protocols including the addition of adolescents and young adults as study participants prompting further investigation into reduction in chemotherapy and RT based on response to initial treatment in more advanced-stage patients. In both studies, there was significant improvement in protocol compliance with respect to RT using pretherapy review of RT data; however, interestingly, there was a significant discrepancy in determining response between site and

study investigators as defined by both anatomical and metabolic imaging reflecting the need for central review of imaging objects to make certain that there was uniformity in response assessment (50% discordance). At this time, the Children's Cancer Study Group (CCG) performed a study randomizing the use of RT in patients with HL similar to POG 8725 and found that the use of RT improved event-free survival at 10 years (91.2%/82.9%, $P = .004$) with no statistical benefit to overall survival validating previous CCG studies.[7–10]

In 2000, the 4 pediatric groups, POG, CCG, Intergroup Rhabdomyosarcoma Study Group (IRSG), and the National Wilms Tumor Study (NWTS) Group, merged to form the COG. This enabled increased accrual to studies with common objectives and introduced risk and response adaptive strategies as secondary points of randomization. Protocol AHOD0031 evaluated intermediate-risk patients with risk-adaptive evaluation using anatomical and metabolic imaging after 2 cycles of ABVE-PC (doxorubicin, bleomycin, vincristine, etoposide, prednisone, and cyclophosphamide). Patients who were deemed to have an RER received 2 additional cycles of chemotherapy and were reevaluated. Those who had a complete response (CR) were further randomized to no RT or 21 Gy RT to involved-field RT (IFRT). Patients with <CR received IFRT.[11]

The SERs were randomized to receive 2 additional cycles of ABVE-PC with or without 2 cycles of dexamethasone, etoposide, cisplatin, and cytarabine (DECA) chemotherapy. Involved-field RT was given to all SER patients. The results again were positive with no difference in survival at 4 years between the RER and SER patients. Event-free survival for RER patients with CR was not statistically improved with RT (87.9%/84.3%, $P = .11$) and not statistically different for the SER patients receiving/not receiving additional DECA (79.3%/75.2%, $P = .11$). However, for SER patients who were PET positive at the time of secondary randomization, there was a benefit ($P = .05$) to those who received additional DECA (70.7%/54.6%) implying the need for intensive therapy in this group of patients. All SER and RER patients in partial response after 4 cycles were treated with IFRT. The trial demonstrated the continued impression that early response assessment supported the use of therapy titration and/or augmentation with favorable patients receiving compressed treatment and unfavorable patients receiving more prolonged treatment. In this study, there was central review of imaging and RT objects to assure uniformity in interpretation of response and to make certain that the RT was delivered per protocol.[12–14]

The success of these studies has prompted similar investigations into subsets of patients with HL including very-limited-stage young patients and patients with advanced stage at presentation. As we begin to study smaller and more clinically specific subsets of patients, international participation will be essential to power studies appropriately for outcome analysis. These include assigning young patients with excised lymph nodes and no residual disease to observation. Advanced-stage patients would be assigned to extended chemotherapy and RT to original sites of bulk disease and sites which demonstrate a more limited response to chemotherapy. These protocols are designed to tailor therapy to the patient and balance the need for disease control and normal tissue outcome. Quality assurance will be essential to answer important study questions in these subgroups of patients. It is important that the patient eligibility is confirmed and all the protocol-required data elements are available to investigators for primary and secondary study analyses.

In the United States/North America, there has been a distinction between adult and pediatric cooperative groups. Thus, HL clinical trials have been developed through both pediatric and adult prisms and have differences in management.[11,15] In 2014, the NCI transitioned its clinical trials system, the Cooperative Group Program, to the NCTN.[16] Within the NCTN, the adult protocols conducted through Alliance for Clinical Trials in Oncology, SWOG, and ECOG-ACRIN have made contributions to our understanding of the disease and disease management. In the adult group studies, efforts have evaluated intermediate- and advanced-stage patients with emphasis on chemotherapy. Recent studies evaluate the role of adaptive therapy with PET to adjudicate secondary therapy pathways similar to the COG intermediate-risk protocol. Alliance/CALGB protocols 50604 and 50801 evaluated chemotherapy attenuation and continuation with and without RT and response assessment using PET.[17–19] ECOG 2496 evaluated the Stanford 5 regimen with ABVD and RT delivered to the mediastinum (bulk) in all patients.[20] The patient study group for ECOG 2496 had intermediate- and high-risk features. The study demonstrated no benefit to more comprehensive chemotherapy and it is important to acknowledge that not all sites of involvement were treated with RT in these patients. SWOG 0816 likewise used PET in the evaluation of intermediate- and advanced-risk patients' therapy adjustment based on response to PET. All patients in this study had stage III and IV HL.[21] Most of the adult groups in the NCTN including the Aids Malignancy Consortium participated in this trial that evaluated an interim PET study after 2 cycles of ABVD chemotherapy. If the interim study was negative (Deauville 1-3: 82% of the study population), patients were then treated with an additional 4 cycles of ABVD. If the study was positive after 2 cycles (18% of the study population), the patients received 6 cycles of escalated BEACOPP. Of those who were PET positive after 2 cycles of ABVD, 11 of 60 patients declined to switch to BEACOPP. The 2-year progression-free survival for PET-negative patients was 79% and for the PET-positive patients was 64%. Not unexpectedly, both hematologic and nonhematologic toxicities were greater in the BEACOPP group. Although the authors comment on the improvement in outcome, there is also opportunity for continued process improvements to further optimize patient outcome. The currently active COG protocol AHOD1331 treats all patients with 5 cycles of ABVE-PC chemotherapy with/

without brentuximab vedotin for advanced HL and is using consolidation RT to areas of limited response and bulk mediastinal disease at presentation with incremental boost RT to areas that remain PET active after cycle 5.[22] In the GHSG HD15 trial, providing RT to areas of limited response in advanced-stage HL occurred in 11% of the patient population. In the current open advanced-stage COG trial, the number of patients receiving RT will be significantly higher because bulk mediastinal disease at presentation is a criterion for postchemotherapy RT.[23]

For the NCTN Network Groups in the United States and North America, the segregation of protocols between the COG and the adult groups has led to an interesting and unfortunate dichotomy for the adolescent patient.[11,15] These patients are treated in a different manner depending on whether they receive care from a pediatric or an adult medical oncologist. Pieters et al[24] skillfully detailed the differences in treatment for the adolescent between the pediatric and the adult protocols including normal tissue volume with consolidation RT. The paper articulates differences in management including longer duration of chemotherapy and potentially wider-volume RT when applied in adult group protocols. Efforts to reconcile this issue to date have not been successful within the NCTN, and although a pediatric/adult integrated trial is currently active for soft tissue sarcoma, there has yet to be a hybrid trial in the United States and North America that includes all patients on a single study in an age-agnostic manner like European colleagues. The current status quo will be rate limiting when trials evaluating subsets of patient population. In comparison, this is the strength of the clinical trials conducted by European allies who evaluate patients with HL in a more age transparent manner.

HL Clinical Trials: European Union and GHSG

Many outstanding and pivotal studies have been completed by European investigators. Groundbreaking work was completed by Bonadonna and colleagues[25] with the introduction of ABVD for clinical care. This served to limited acute toxicity and late effects from management and prompted a new generation of clinical trials using ABVD alone for early-stage disease and strategies using hybrid chemotherapy for patients with intermediate and advanced risk factors. The contributions have led to important process improvements in patient care.

In 1978, the GHSG was established. The administrative structure provides support for clinical trial activity including data acquisition and data management. The objective was to develop HL studies that were timely and addressed important questions of the day. To date, GHSG has developed 18 primary studies and several additional studies that have addressed issues with refractory and recurrent disease. The initial studies included early-, intermediate-, and advanced-stage patients and carefully evaluated multiple chemotherapy programs and options in the strategic application of RT to varied target dose and volume. As the group matured, protocols were designed to specific subgroups. There have been many notable and important publications by this group. In protocol HD7, the GHSG confirmed the importance of chemotherapy in early-stage disease. Patients treated with chemotherapy (ABVD) and RT had improved freedom from treatment failure than those treated with RT alone (88%/67%). Protocol HD8 established that consolidation IFRT in early-stage patients with unfavorable features was as effective as and less toxic than extended volume RT. In HD9, COPP-ABVD, standard dose BEACOPP, and escalated dose BEACOPP were evaluated in patients with advanced-stage disease. The freedom from failure rate was 69%, 76%, and 87%, respectively, statistically favorable to escalated BEACOPP with uniform overall survival in all groups. This study shifted the discussion to an important area. Although there was greater toxicity with dose-escalated BEACOPP (increased etoposide), should we accept a potentially lower primary control rate understanding that (1) patients could be rescued with additional therapy and (2) toxicity may be lower for patients not receiving extended chemotherapy. The protocol raised fundamental questions concerning the dilemma between toxicity and tumor control and established a series of protocols evaluating the role of BEACOPP in several protocols. HD11 did not establish that BEACOPP and 20 Gy RT were better than ABVD and 30 Gy RT in patients with early-stage disease with unfavorable features, therefore challenging the role of more intensive chemotherapy in this cohort of patients and maintaining that 30 Gy RT was preferable to 20 Gy RT in this setting. The COG trials currently use 21 Gy RT. Reducing toxicity and maintaining efficacy in advanced-stage HL were the objectives of HD12 with reduction in BEACOPP after 4 cycles of escalated BEACOPP. The results were sobering because toxicity was not improved and efficacy decreased, again suggesting that intensification of therapy was an advantage for disease control with the continued expense of toxicity despite dose reduction. Intensification with 2 cycles of BEACOPP and 2 cycles of ABVD plus 30 Gy RT was superior to ABVD plus 30 Gy RT for early unfavorable patients in HD14. There was more toxicity with intensification, however, no increase in mortality and second malignancies. HD15 introduced PET-guided therapy for advanced-stage patients and evaluated 8 versus 6 cycles of dose-escalated BEACOPP with RT applied to areas of limited response based on anatomical and metabolic imaging. About 11% of patients received RT on this trial. Six cycles were compared favorably with 8 cycles, and the negative predictive value of PET was 94%. The study solidified the impression that chemotherapy dose escalation was superior but the number of cycles could be reduced and not compromise outcome using PET as a tool to adjudicate the approach.[22,23,26–31]

The GHSG has excellent processes in place that can acquire protocol information including imaging and RT objects similar to quality assurance offices in the United States. The GHSG studies have included therapy attenuation for early-stage patients and patients with early response to treatment who

have more advanced disease at presentation. Early studies supported the use of RT as consolidation treatment and over time demonstrated the advantage of decreasing the RT volume and dose, based on response and disease location at presentation. More recent studies have adjusted the application of RT to specific areas of limited response and bulk at presentation. This concept is under evaluation in North American clinical trials as well.

These concepts were likewise supported in part by a recent study completed by fellow European colleagues[32] evaluating the use of ABVD and BEACOPP 4×4 in patients with intermediate and advanced risk features. The study demonstrated findings similar to GHSG investigators that ABVD and dose-adjusted BEACOPP for etoposide demonstrated no clear advantage to de-escalated BEACOPP. The data treating patients with dose-escalated BEACOPP in the GHSG with 6 cycles of escalated therapy with/without RT remain the strongest information to date for freedom from failure. There may, however, be no increase in overall survival as those who fail primary management to date respond to secondary therapy. The objectives of the studies between the United States and the GHSG are asymmetric as the US studies generally began treatment with ABVD with attenuation or intensification driven by response to treatment. The German group established the paradigm to initiate care in advanced-stage patients with more intensive therapy with dose/therapy adjustment to a less-intensive regimen if the patient achieved a good response to initial management. The GHSG investigators demonstrated improved CR and event-free survival rates with more intensive initial therapy and as a consequence established a strategy to limit first-course failure perhaps at the expense of toxicity. American and some European investigators suggest that because patients can be rescued with secondary/relapse therapy, achieving up-front full CR at the expense of toxicity remains less desirable.[33–35] Table 2 summarizes Hodgkin studies.

Assignment of Risk

There are differences between the United States and European investigators in the assignment of risk in protocols. Investigators agree on low-risk patients with favorable features. These generally include patients with stage I and II disease, A status, and no bulk. Patients with stage I and II disease with bulk and selected other features including mixed cellularity histology are often classified as early-stage unfavorable patients in GHSG and European protocols and as intermediate-risk patients in protocols generated in the NCTN/North America. Intermediate-risk patients include stage I and II patients with B symptoms and bulk as well as stage III and IV patients with A symptoms. Advanced-stage III and IV patients include those with bulk and B symptoms for groups in the United States/North America and Europe. There remains a challenge in overlap areas between groups and we will need to be careful in reviewing publications, understanding that there may be differences in clinical trial populations within specific groups.

Influence of Imaging on Clinical Trials in HL

Imaging is an integral component to clinical trials and there is no other disease where imaging has had a larger impact on clinical trial management. Imaging has influenced staging and compressed the time from diagnosis to initiating treatment. The CT and PET are the primary vehicles used for determining response which generate secondary and tertiary points of randomization. The ease of secure image transfer through multiple digital media formats has facilitated this. Web-based tools enable study and site investigators to review imaging in real time.

Historical image interpretation by site investigators was accepted as the standard for trial management. The COG protocol 9426 established the fact that there can be a significant difference in site and central interpretations of response which can obscure trial results. Study groups in North America and Europe are now routinely place high importance on imaging, embedding imaging in clinical trials for staging, defining and adjudicating response, and assessing treatment failure.

With the ease of digital data transfer, the international treatment community is provided with a rare opportunity to integrate clinical trial strategies and collaborate in a manner previously impossible to achieve. Of equal importance, quality assurance centers recognize that image quality is improving worldwide, imaging colleagues are performing volumetric CT imaging and PET studies with the timing and vigilance required by protocol, and imaging acquisition strategies are well established. This has changed clinical trials management, permitting real-time central review with site and study investigators. This permits harmonization of interpretation of response and ensures that the patient is assigned to the correct protocol and that response to therapy is interpreted in a uniform manner. Disease recurrence/progression can be done in a collaborative manner, and all important decisions that are essential for clinical trial management can be accomplished by consensus management. This harmonization will serve to facilitate international trial participation moving forward.

Early-Stage Favorable Patients

This group of patients has undergone extensive evaluation over the past several decades. Studies have demonstrated that therapy titration driven by response is an acceptable therapeutic strategy for North American and European trial groups. We have evidence from these investigators that ABVD and alternative chemotherapy given in less than 4 cycles along with strategically limited volume RT is curative in most of the patients. International collaboration will help us evaluate different and perhaps more limited chemotherapy agents and assess patterns of failure to better understand the role of local therapy in these patients. There is no fundamental disagreement between European and North American investigators on this point and international cooperation will permit study of this selected patient cohort.

Table 2. Hodgkin lymphoma protocol summary.

TRIAL	AGE, Y	DISEASE STAGE	TREATMENT	STUDY STATUS	OUTCOME
POG 8725	≤21	IIB, IIIA2, IIIB, IV	Alternating MOPP-ABVD×8±low-dose TNI	Completed	5, 6
COG 9426	≤21	IA, IIA, IIIA1	Response-based: DBVE×2±DRZ—evaluation CR: IFRT PR, SD: DBVE×2±DRZ+IFRT	Completed	7, 36
COG 9425	≤21	IB, IIA/IIIA1 with LMA or IIIA2; IIB, IIIB, IV	Risk-adapted, response-based: ABVE-PC×3—evaluation RER: 21 Gy RT to regional fields SER: ABVE-PC×2+21 Gy RT	Completed	8, 37
COG AHOD0031	<21	Stages IB, IA/IIA with bulk, IIB, IIIA, IVA	Response-adaptive therapy: ABVE-PC×2—evaluation RER: ABVE-PC×2—evaluation RER, CR: randomized to IFRT/no therapy RER<CR: IFRT SER: IFRT+ABVE-PC×2±DECA×2	Completed	11, 12, 38
COG AHOD1331	2-22	Stages IIB, IIIB-IVB	ABVE-PC×5±brentuximab vedotin Consolidation RT to areas of limited response, bulk mediastinal disease at presentation+incremental boost RT to PET+areas after cycle 5	Currently recruiting	22
CALGB/ Alliance 50604	18-60	Stage I/II nonbulky	ABVD×2−PET PET−: ABVD×2 PET+: BEACOPP (escalated)×2+3060 cGy IFRT	Ongoing, not recruiting	18, 39, 40
CALGB/ Alliance 50801	18-60	Bulky stages I/II	ABVD×2 PET−: ABVD×6 PET+: BEACOPP (escalated)×4+IFRT	Ongoing, not recruiting	19
ECOG 2496	≥16	Stage I-IIA/B+massive mediastinal adenopathy; stage III/IV	ABVD compared with Stanford V (±) RT	Completed	20, 41

Table 2. (Continued)

TRIAL	AGE, Y	DISEASE STAGE	TREATMENT	STUDY STATUS	OUTCOME
SWOG 0816	18-60	Stages III, IV	ABVDv2—PET/CT PET/CT—ABVD×4 PET/CT+BEACOPP (escalated)×6	Ongoing, not recruiting	21, 42
GHSG HD7	16-75	Stages I, II without risk factors	ABVD×2+30 Gy EF+10 Gy IF compared with RT alone (30 Gy EF+10 Gy IF)	Completed	
GHSG HD8	16-75	Stages I and II with ≥1 risk factors; stage IIIA—risk factors	COPP/ABVD×2+30 Gy EF (10 Gy on bulk) or 30 Gy IF (10 Gy on bulk)	Completed	27
GHSG HD9	15-65	Stages IIB, IIIA+risk factor; stage IIIA+risk factor; stages IIIB, IV	COPP/ABVD×4 BEACOPP (baseline)×8 BEACOPP (escalated)×8 RT, if necessary (30 Gy on bulk, 40 Gy on residual tumor)	Completed	28
GHSG HD11	1 Gy6-75	Stages IA, IB, IIA+risk factor; IIB+risk factor	ABVD×4+30 Gy IFRT ABVD×4+20 Gy IFRT BEACOPP (baseline)×4+30 Gy IFRT BEACOPP (baseline)×4+30 Gy IFRT	Completed	29, 43
GHSG HD12	16-65	Advanced stages IIB+risk factors III, IV	BEACOPP (escalated)×8±RT BEACOPP (escalated)×4+BEACOPP (baseline)×4±RT	Completed	30, 44
GHSG HD14		Stage IA, IB, IIA+risk factor; stage IIB+risk factor	ABVD×4+30 Gy IFRT BEACOPP (escalated)+ABVD×2+30 Gy IFRT	Completed	31
GHSG cHD15	18-60	IIB+large mediastinal mass or extranodal lesions; stages III and IV	BEACOPP (escalated)×8 BEACOPP (escalated)×6 BEACOPP 14×8 30 Gy RT to residual, PET+lesions	Completed	45

Abbreviations: ABVD, doxorubicin, vinblastine, bleomycin, dacarbazine; ABVE-MOPP, Adriamycin (doxorubicin), bleomycin, vinblastine, dacarbazine—mechlorethamine, oncovin (vincristine), procarbazine, prednisone; ABVE-PC, doxorubicin, bleomycin, vincristine, etoposide, prednisone, cyclophosphamide; BEACOPP, bleomycin, etoposide, Adriamycin, cyclophosphamide, vincristine, procarbazine, prednisone; CR, complete response; DBVE, doxorubicin, bleomycin, vincristine, etoposide; DRZ, dexrazoxane; EF, extended field; IFRT, involved-field radiation therapy; PET/CT, positron emission tomography and computed tomography scan; PR, partial response; RER, rapid early responder; RT, radiation therapy; SD, stable disease; SER, slow early responder; TNI, total nodal irradiation.

Early-Stage Unfavorable Patients

This is an important group of patients who have features at presentation that may appear less favorable. Patients who demonstrate an excellent response to induction chemotherapy may benefit from therapeutic titration. Often these patients have stage I and II disease with bulk. European investigators have studied this population which has not been as visible in NCTN trials as these patients have uniformly been considered intermediate risk. With an international trial, this subgroup could be made more visible, empowered by collaboration to meet accrual objectives and establish common pathways for trial management.

Intermediate-Risk Patients

In NCTN clinical trials, intermediate-risk patients often include patients who would otherwise be considered early-stage unfavorable patients in European trials. These patients are also excellent candidates for clinical trials that adjust therapy based on response similar to the intermediate-risk clinical trial COG AHOD0031. The recent EORTC and AHOD0031 trials have provided evidence that response to induction therapy can permit therapy titration in this cohort of patients. This group generally includes patients with IIB disease and patients with stage III and IVA disease. European studies have shown that ABVD and de-escalated BEACOPP demonstrate similar results in this setting with RT. AHOD0031 demonstrated that patients who had an RER to 2 cycles of chemotherapy and a CR to 2 additional cycles as defined on response imaging appear to have an equally good outcome whether or not the patients underwent consolidation RT with data published at 3 years. The study also demonstrated an advantage to patients who underwent more extended and aggressive chemotherapy who were deemed an SER and were PET positive on response imaging. Therefore, this is a diverse group of patients which can be differentiated by biological response to treatment validated by response to treatment using modern imaging tools. International protocols can be directed with multiple tiers of evaluation based on response to chemotherapy. This may prove to be a good strategy to expedite completion of trials and permit further evaluation of patients with varied response to induction therapy including additional therapy to patients who do not exhibit a CR to chemotherapy treatment. Therapies can be further titrated based on rapidity of response or augmented as needed if the response to initial therapy is protracted. The group with more delayed response requires process improvements as freedom from failure remains less than those who respond more rapidly despite the augmentation of therapy. This would include new agents including those directed to CD30 and new biologic therapies similar to patients with high-risk disease.

High-Risk Patients

This patient cohort often has large and diffuse tumor burden at presentation including bone marrow and visceral disease and often has B symptoms. The most visible separation in practice strategy between colleagues in Europe and North America is seen in this group. Colleagues in the GHSG would initiate care with dose augmentation and potentially revisit dose reduction in chemotherapy based on response. North American investigators would consider approaches to care that may invite dose intensification induction therapies in high-risk patients; however, most protocols would move forward with strategies similar to intermediate-risk patients with dose augmentation therapies based on response to treatment. The arguments are dose augmentation as initial therapy will decrease secondary treatment due to relapse. North American investigators will argue that survival rates can be improved by secondary therapy at the time of relapse therefore limiting toxicity to patients who do well with less-intensive induction therapy. Protocols can be developed to test this hypothesis. Even with initial dose escalation, relapse rates need and can be improved and new biologic therapy including application of RT as in COG protocol AHOD1331 can be used to address disease progression rates. International clinical trial participation will serve to better harmonize treatment strategies. We have important work to do in this cohort of patients as freedom from failure rates remain suboptimal especially in patients who do not respond to initial therapy.

Radiation therapy

The role of RT has evolved over time. Early phase management gave relatively high-dose RT to extended volumes of tissue in the initial effort to control tumor. As evidence of treatment-related complications and second malignancies became more visible, efforts at radiation dose/volume modification and therapeutic titration became embedded in clinical trials in both Europe and the United States/North America. In patients with low-risk disease, both European and NCTN investigators have evaluated the role of decreasing cycles of chemotherapy with attenuated dose of RT directed to sites of disease at presentation as defined on imaging. Patients with a CR to chemotherapy may not require RT and this will be an important study point moving forward. Early- and intermediate-risk patients with CR to chemotherapy as defined by metabolic imaging also may not require RT. It is now clear that when RT is applied to patients with favorable outcome, only the sites of disease at presentation need to be treated to a dose in between 20 and 30 Gy based on the clinical situation. Lower doses are generally applied to protocols originating in the COG and higher doses in the adult NCTN groups and the GHSG. Protocols in advanced-stage patients evaluate the role of RT directed to areas at presentation that do not fully respond to chemotherapy. The COG trials in this cohort of patients are including RT to sites of bulk disease at presentation (mediastinum) with dose augmentation to sites of persistent activity on PET after cycle 5 of chemotherapy. In European/GHSG protocols, approximately 11% of high-risk patients will receive RT to sites that do not fully respond to chemotherapy as defined

on imaging. In the current COG advanced-risk patients, the percent of patients undergoing RT will be considerably higher as bulk disease at presentation is a criterion for treatment. Clinical trials will help answer these questions moving forward. As part of clinical trial design, the patterns of relapse will be important to study to best determine the value of RT in all risk categories.

Quality Assurance

One area of alignment between European and North American colleagues is quality assurance including RT. As previously indicated, North American trial protocol POG 8725 evaluated patients with intermediate-, early-, and advanced-stage features with 8 cycles of hybrid chemotherapy including MOPP-ABVD with RT to all sites of original disease as the point of randomization. The data were reviewed in retrospect after treatment had been completed. The study deviation rate was 30% and all deviations were due to nonprotocol coverage of disease sites at presentation. Patients who received RT per protocol guidelines had a 10% survival advantage to those who received chemotherapy alone. Because data transmission tools were becoming more nimble with digital media, the next series of clinical trials in COG required real-time pretreatment review of treatment objects. This experience decreased the RT deviation rate to less than 5%. However, these protocols required adjustment in treatment based on response and it was found that central review of objects disagreed with site review more than 50% of the time in a pre-PET era of clinical trials. AHOD0031 required central review of imaging and RT objects in real time to manage secondary and tertiary trial randomization. This trial successfully managed real-time review of objects in more than 1700 patients with data reviewed at multiple time points during the course of this important study. Similar experience was seen by the GHSG recognizing the importance of quality assurance in trial outcome. If patients are not treated in a uniform format, the results of the trial can be deceiving as was seen in POG 8725. The GHSG likewise has carefully monitored quality assurance for RT in their portfolio of trials and have published information demonstrating that adjustments were required in RT treatment plans in more than 50% of patients on early- and intermediate-stage protocols.[27] There are protocols, however, where quality assurance may not play as crucial a role. As can be seen in POG 8725, excluding areas of disease eliminated any advantage seen by RT. In the GHSG, advanced-stage protocol only selected areas were treated with RT and intentionally did not include all areas of disease at presentation. In this protocol, quality of RT/compliance to recommendations did not affect trial outcome. Modern protocols are asking questions concerning the role of RT and what specific volumes and dose to treat based on response to initial therapy. Quality assurance will be important moving forward to see whether these unique questions can be addressed in a clinical trial format and will require central review in real time to make certain that treatment is applied per intent of the protocol.

Summary

As clinical trials have matured, patient management strategies between investigators in Europe and North America have become more aligned. Methods of staging have become more uniform. Because of near-immediate ability to transfer imaging and RT objects for central review, it is now feasible to easily manage HL clinical trials on a worldwide basis. Although there are differences in how patients are assigned into categories, investigators are aligned in therapeutic titration for favorable patients with early and intermediate risk features who demonstrate excellent response to initial chemotherapy. The ability to have information reviewed on a real-time basis will permit specific subsets of patients to be evaluated. This would include clinical trials in the very-young and very-early-stage patients with single lymph node involvement that is fully excised and older patients whose medical comorbidities require nontraditional approaches to management. High-risk patients require more study. Outcomes for these patients remain suboptimal with need for improvement, especially in patients with more limited response to initial therapy. Patient care in this subgroup continues to be asymmetric with GHSG investigators favoring more intensive therapy to limit relapse with North American and some European investigators favoring less-intensive initial therapy with dose augmentation if patients do not respond well to initial care. International registries with shared quality assurance responsibilities housed within established centers can function at an enterprise level to make certain that normal tissue tolerance and second malignancies are carefully tracked and correlated to the chemotherapy and RT treatment plan. It will also be important for the NCTN to align the adult and pediatric groups into single protocols and not separate groups for adults and children. As indicated, adolescents are fragmented in their care with this approach and European colleagues do not have this point of distinction. Adolescents and adults are treated in an identical manner by European colleagues and aligning the NCTN into a single strategy for management of HL will help facilitate accrual and meet clinical trial objectives for specific subsets of patients. This strategy also would facilitate completion of trials with new therapies aligned with specific biomarkers for those patients who do not succeed with primary management. We now have an opportunity to improve the management of these patients, and moving forward with worldwide trials will greatly improve our understanding of this disease and enhance patient management.

Author Contributions

TJF conceived and designed the experiments, analyzed the data, wrote the first draft of the manuscript, agree with manuscript results and conclusions, and jointly developed the structure and arguments for the paper. TJF and MB-J contributed to the writing of the manuscript, made critical revisions and approved final version, reviewed, and approved the final manuscript.

Disclosures and Ethics

As a requirement of publication, authors have provided to the publisher signed confirmation of compliance with legal and ethical obligations including but not limited to the following: authorship and contributorship, conflicts of interest, privacy and confidentiality, and (where applicable) protection of human and animal research subjects. The authors have read and confirmed their agreement with the ICMJE authorship and conflict of interest criteria. The authors have also confirmed that this article is unique and not under consideration or published in any other publication, and that they have permission from rights holders to reproduce any copyrighted material. Any disclosures are made in this section. The external blind peer reviewers report no conflicts of interest.

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