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Guest Editor

Bruce D. Cheson, MD, FACP

Head of Hematology
Lombardi Comprehensive
Cancer Center
Georgetown University Hospital
Washington, DC

Faculty

Volker Diehl, MD

Professor of Medicine
University of Cologne
Cologne, Germany

Anas Younes, MD

Professor
The University of Texas
M. D. Anderson Cancer Center
Houston, TX

John Radford, MD

Professor of Medicine and Oncology
Christie Hospital
University of Manchester
Manchester, United Kingdom

Hodgkin Lymphoma: Advancing Beyond Standard Management

A Review of a Satellite Symposium Held in Conjunction With the 10th International Conference on Malignant Lymphoma
June 4–7, 2008
Lugano, Switzerland

Guest Editor: Bruce D. Cheson, MD, FACP

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Statement of Need

Although more than 80% of patients with Hodgkin lymphoma can be cured, significant challenges remain for physicians treating this disease. Because of the exceptional expected lifespan of patients treated for Hodgkin's lymphoma, inducing the fewest irreversible toxicities and late complications of treatment, such as infertility and secondary neoplasms, are of paramount importance. Additionally, identifying and effectively treating recurrence in those who are not cured remains a major concern. Patients who relapse after chemotherapy have only a 20% cure rate with salvage therapy. New chemotherapy regimens, as well as the use of biologic agents, are under investigation as potential means by which toxicity can be reduced and cure rate can be improved. The use of risk-directed therapy to guide treatment decisions is another approach that may help accomplish both of these goals. 2-[18F]fluoro-2-deoxy-D-glucose (FDG) and positron emission tomography (PET) (FDG-PET) imaging after completion of therapy can divide patients into high- and low-relapse risk categories. In this way, only those patients with a high probability of relapse will receive intensive therapy, while those who do not are spared the additional toxicity associated with these regimens. Participants of this activity will not only be able to understand and apply current guidelines, but they will also gain an awareness of the novel investigational agents and regimens that are being tested in patients with Hodgkin lymphoma.

Target Audience

This activity is intended for hematologists, oncologists, physicians, physician assistants, and other healthcare professionals interested in the treatment of patients with hematologic malignancies, specifically Hodgkin's lymphoma.

Educational Objectives

Upon completion of this activity, healthcare professionals will be able to

1. Describe the standard therapies currently used to treat both newly diagnosed and relapsed/refractory Hodgkin's lymphoma.
2. Summarize current combination chemotherapy regimens used to treat Hodgkin's lymphoma.
3. List biologic agents that are currently under investigation in phase II clinical trials for the treatment of Hodgkin's lymphoma.
4. Assess the usefulness of risk-directed therapy guided by FDG-PET for the management of Hodgkin's lymphoma.

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Hodgkin Lymphoma: Advancing Beyond Standard Management

A Review of a Satellite Symposium Held in Conjunction with the 10th International Conference on Malignant Lymphoma, June 4–7, 2008, Lugano, Switzerland

Survival of patients with Hodgkin lymphoma (HL) has shown a significant improvement over the last 40 years (Figure 1). Prior to the mid 1900s, HL was fatal for most patients. In the 1970s, the first effective chemotherapy regimen in HL was MOPP (mechlorethamine, vincristine, procarbazine, prednisone), but it was associated with infertility, an unacceptable risk of leukemia, and other secondary malignancies.[1]

Regimens such as ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) represented a major advance in patient care because of improvement in survival with a reduction in treatment-related complications. The advent of dose-intense chemotherapy protocols such as Stanford V (mechlorethamine, doxorubicin, vinblastine, vincristine, bleomycin, etoposide, prednisone), MEC (mechlorethamine, CCNU, vindesine, melphalan, prednisone, epidoxorubicin, vincristine, procarbazine, vinblastine, bleomycin), and BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone) further enhanced patient management. However, the need persists for improved standard of care with a more effective regimen and a more favorable toxicity profile. New agents with potential for both initial treatment and for relapsed and refractory diseases are in development. In addition, risk-adapted patient management using [^{18}F]-fluorodeoxyglucose positron emission tomography (FDG-PET) is becoming evaluated. This technology, in combination with new therapies, will further improve the outcome for patients with HL.

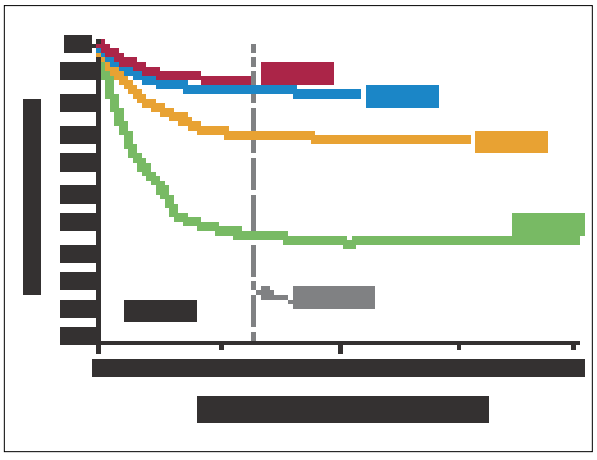

Figure 1. Hodgkin lymphoma survival characteristics by era.

The Standard Approach to the Treatment of Hodgkin Lymphoma

Bruce D. Cheson MD, FACP, Head of Hematology at the Lombardi Comprehensive Cancer Center, Georgetown University Hospital, Washington, DC, reviewed the incidence and histologic characteristics of HL variants and presented the historical background of patient management since the mid-1960s.

HL includes classic HL (cHL) and nodular lymphocyte predominant (NLP) HL, with cHL being the most common variant, accounting for 85–90% of all cases of HL; 65% are of the nodular sclerosing histologic subtype, 20% mixed cellularity, 5% lymphocyte-rich, and 2% lymphocyte-depleted subtypes. The cHL and NLP subtypes differ in many morphologic and immunologic features. The morphologic appearance of cHL tends to be diffuse with an interfollicular nodular pattern, whereas NLP is nodular. The cHL subtype is characterized by Reed-Sternberg cells, occasionally with lacunar variants, with a background consisting of lymphocytes, eosinophils, plasma cells, and histiocytes. T cells are present in greater numbers than B cells. On the other hand, the NLP subtype has lymphocytic and histiocytic (L&H) cells, or "popcorn" cells. It is the reverse for NLP, where B cells are predominant. The immunophenotype for cHL tends to be positive for CD15 and CD30, and mostly negative for CD20 and epithelial membrane antigen (EMA). It is the converse for NLP, where the immunophenotype is negative for CD15 and CD30, positive for CD20 and EMA.[2] Finally, the Epstein-Barr virus is detected in Reed-Sternberg cells of cHL, particularly in the mixed cellularity variant, but rarely in the L&H cells of NLP disease.[2]

Table 1. Randomized Trials With ABVD

Group/ Regimen	Pts	Stages	FFP, %	Yrs
Milan[4]	76	IIB, III, IV		10
ABVD			63	
MOPP			50 (NSD)	
Milan[5]	232	IIB, III, IV		7
ABVD + RT			81 (*P*<.002)	
MOPP + RT			63	

ABVD=doxorubicin, bleomycin, vinblastine, and dacarbazine; FFP=freedom from progression; MOPP=mechlorethamine, vincristine, procarbazine, prednisone; RT=radiotherapy.

The Development of ABVD as Standard of Care: A 40-year Clinical Journey

Before the 1960s, the median survival for patients with HL was approximately 1 year; 5-year survival stood at a mere 5%. In 1964, DeVita and colleagues introduced MOPP, which cured about 50% of patients with advanced-stage disease (ie, stages III and IV) but was associated with unacceptable toxicities such as sterility, gastrointestinal and neurologic symptoms, and, of most concern, a high risk of secondary malignancies.[3] In the mid-1970s, Bonadonna and colleagues developed the ABVD regimen for MOPP failures.[4] The acute toxicities associated with ABVD were more tolerable than those experienced with MOPP, but the delayed toxicity profile still included pulmonary effects associated with bleomycin. Two early studies comparing ABVD with MOPP showed a prolonged failure-free survival (FFS) with both regimens, but only one study that investigated the regimens in advanced stage disease was large enough to demonstrate a significant difference in favor of the ABVD.[5] In that study, reported by Santoro and colleagues, 232 previously untreated patients received 3 cycles of either combination, followed by extended field to total nodal irradiation, depending on sites of nodal involvement. The complete remission (CR) rate was 81% following MOPP and 92% following ABVD (*P*<.02). At 7 years of follow-up, ABVD demonstrated superior efficacy to MOPP in terms of freedom from progression (FFP, 81% vs 63%; *P*<.002), relapse-free survival (88% vs 77%; *P*=.06), and overall survival (OS, 77% vs 68%; *P*=.03; Table 1). Then followed a decade of clinical research that evaluated variations of MOPP/ABVD sequences in an attempt to identify a superior regimen. Cumulative results from 6 large randomized, prospective, multicenter studies in more than 2,000 patients comparing MOPP/ABV(D) with MOPP alone showed consistent results: the complete response rate, FFS, and OS all favored the anthracycline-containing regimens over MOPP alone.[4,6-10]

Several groups continued to evaluate MOPP and ABVD combinations. Viviani and colleagues conducted a prospective randomized trial in which the efficacy of 2 different MOPP and ABVD chemotherapy sequences were compared in untreated HL (stages IB–IV).[11] Patients were randomized to receive either the alternating regimen (1 cycle of MOPP monthly alternated with 1 cycle of ABVD) or the hybrid regimen (a half cycle of MOPP alternated with a half cycle of ABVD within a 1-month period). Both sequences of MOPP and ABVD were administered for a minimum of 6 cycles, followed by radiotherapy to sites of pretreatment bulky disease. The CR rate was 91% with the alternating regimen and 89% with the hybrid regimen. At 10 years, the FFP rate was 67% versus 65%, and the OS rate was 74% versus 72% for the alternating and hybrid regimens, respectively, thus failing to demonstrate superiority for either regimen.

Connors and colleagues from the National Cancer Institute of Canada conducted a prospective, randomized trial comparing a MOPP/ABV hybrid regimen with alternating courses of MOPP and ABVD.[12] Eligible patients were either untreated and with advanced disease (stage IIIB, IVA, or IVB) or previously treated with wide-field radiation. Response rates to the 2 regimens were similar. Five-year OS rates were 81% for MOPP/ABV hybrid and 83% for alternating MOPP/ABVD (*P*=.74; 95% confidence interval [CI], -11–7). Five-year FFSs were 71% for MOPP/ABV hybrid and 67% for alternating MOPP/ABVD (*P*=.87; 95% CI, -9–17). A planned subset analysis failed to demonstrate a difference in response for either regimen for newly diagnosed patients (5-year FFS rates were 70% for MOPP/ABV hybrid and 59% for alternating MOPP/ABVD; *P*=.180). In contrast, the alternating MOPP/ABVD regimen showed a superior outcome in patients with prior irradiation, with a 5-year FFS of 94% versus 73% for MOPP/ABV hybrid (*P*=.017). The authors concluded that the 2 regimens were comparable in this patient population.

The North American Intergroup Study led by the Eastern Cooperative Oncology Group (ECOG) randomized 737 patients with previously untreated HL or those in first relapse following radiotherapy, to either 6–8 cycles of a sequential regimen of MOPP-ABVD followed by 3 cycles of ABVD or 6–12 cycles of a MOPP/ABV hybrid.[13] The overall response rate (ORR) was 95%, with CR in 79% of patients; 83% on the MOPP/ABV hybrid and 75% on the sequential MOPP/ABVD arm (*P*=.02). The 8-year FFS rates (median follow-up time of 7.3 years) were 64% for MOPP/ABV hybrid and 54% for sequential MOPP/ABVD (*P*=.01). The 8-year OS

rate was significantly better for the MOPP/ABV hybrid (79%) compared with sequential MOPP/ABVD (71%; *P*=.02). The MOPP/ABV hybrid group experienced more life-threatening or fatal neutropenia and pulmonary toxicity than the sequential MOPP/ABVD arm, which was associated with significantly greater thrombocytopenia. Nine cases of acute myelogenous leukemia (AML) or myelodysplasia (MDS) were reported in the sequential regimen compared with only 1 in the hybrid (*P*=.01). Thus, the MOPP/ABV hybrid was more effective than sequential MOPP/ABVD, with an improved FFS and OS and a more favorable toxicity profile.

Two additional studies conducted in North America further defined the optimal regimen for patients with advanced HL. A critically important study was led by the Cancer and Leukemia Group B (CALGB) and reported by Canellos and associates; it compared MOPP alternating with ABVD, MOPP alone, and ABVD alone in patients with newly diagnosed advanced HL.[7] Patients did not receive additional radiation therapy and those who did not show a CR or who relapsed with either MOPP alone or ABVD alone were eligible to be switched to the opposite regimen. In 361 eligible patients, 123 received MOPP, 123 received MOPP alternating with ABVD, and 115 received ABVD alone. Patients were stratified according to age, stage, previous radiation, histologic features, and performance status. The ORR was 93%, with 77% CR; CR rates for the ABVD-containing regimens were higher: 83% for MOPP/ABVD, 82% for ABVD compared to 67% with MOPP (*P*=.006 for the comparison of MOPP with the other 2 regimens). In an update of the original data as of August 2006, the median event-free survival (EFS) was 2.54, 6.9, and 12.4 years, respectively (*P*=.047), with an OS of 13.9 years, 18.5 years, and not yet reached respectively, according to a personal communication with Dr. Canellos. Moreover, MOPP was associated with more severe toxic effects on bone marrow than ABVD; it also required a greater frequency of dose reductions. There were 2 cases of non–small cell lung cancer with ABVD and 2 with MOPP/ABVD. In addition, there have been 2 reports of AML—1 with MOPP, 1 with MOPP/ABVD, and none with ABVD alone. Furthermore, ABVD was less myelotoxic than MOPP or MOPP/ABVD alternating with MOPP. This study supported ABVD as the standard regimen for advanced HL because it was as effective as MOPP/ABVD, and both regimens were superior to MOPP alone.

The CALGB undertook an additional study comparing ABVD to MOPP/ABV as initial therapy for patients with advanced stage disease.[14] Duggan and colleagues randomly assigned 856 adult patients with advanced HL to either ABVD or MOPP/ABV (days 1 and 8), both administered until CR plus 2 additional cycles. The primary study endpoints were FFS and OS, life-threatening acute toxicities, and serious long-term toxicities. Overall, the efficacy profiles for the 2 treatment groups were very similar; CR (76% vs 80%, *P*=.16), FFS at 5 years (63% vs 66%, *P*=.42), and OS at 5 years (82% vs 81%, *P*=.82) for ABVD and MOPP/ABV, respectively. However, acute pulmonary and hematologic toxicities were significantly more common with MOPP/ABV (*P*=.060 and *P*=.001, respectively). Twenty-four deaths were attributed to initial treatment: 9 with ABVD and 15 with MOPP/ABV (*P*=.057). Twelve secondary malignancies were associated with ABVD, and 24 with MOPP/ABV (*P*=.13). Ten patients developed MDS or AML: 9 who were initially treated with MOPP/ABV, and 1 following ABVD but who subsequently received MOPP-containing regimens and radiotherapy before developing leukemia (*P*=.011). Thus, although both therapies were effective for HL, the more favorable toxicity profile of ABVD further supported this regimen as the standard for the advanced disease.

The Stanford V Program

The Stanford V Program, developed by Horning and colleagues at Stanford University, is a rapidly sequencing chemotherapy strategy that alternates myelosuppressive and nonmyelosuppressive agents on a weekly schedule, and is followed by modified involved field radiation therapy (IFRT) 2–4 weeks after chemotherapy (Table 2).[15] The extent of radiation was determined by the stage of disease (30 Gy for early stage, 36 Gy for bulky disease [ie, ≥5 cm or macroscopic splenic disease]). The original single-institution study included 87 patients with favorable stage I or II disease, 61 with limited stage but bulky disease and 108 with advanced stage disease.[15] The 8-year disease-specific survival was 97%, OS 95%, and FFP 91%. FFP was 96%, 92%, and 86% for the early stage, bulky disease, and advanced stage patient groups, with an OS of 98%, 92%, and 95%, respectively (Figure 2). No patients progressed during the treatment period and no treatment-related deaths were reported. Of note, there were no cases of secondary AML/MDS or non-Hodgkin lymphoma, and 25% of patients conceived healthy infants post-treatment. The toxicity of the regimen was manageable and the majority of relapsed cases were treated successfully.

To better characterize the efficacy of the Stanford V regimen in a multicenter setting, Federico and colleagues randomized patients to either 6 cycles of ABVD, 12 cycles of a modified Stanford V, or 6 cycles of MEC.[16] In addition, radiotherapy was given to 2 or fewer partially responding sites of previous bulky disease. The CR for ABVD, Stanford V, and MEC were 89%, 76%, and 94%, respectively. Five-year FFS was 78%, 54%, 81%, respectively; progression-free survival (PFS) rates were 85%, 73%, and 94%, respectively. Stanford V was

Table 2. The Stanford V Chemotherapy Regimen

Note: consolidative irradiation (36 Gy) is given to sites of disease with maximum transverse diameter of ≥5 cm or macroscopic splenic disease, commencing with week 14–16.

*Doses reduced during weeks 10 and 12 for patients age ≥50 years as indicated in text.

†Dose capped at 2 mg.

		Week											
Drug	**Dose (mg/m²)**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Doxorubicin	25	3		3		3		3		3		3	
Vinblastine	6*	3		3		3		3		3		3	
Nitrogen mustard	6	3				3				3			
Vincristine†	1.4		3		3		3		3		3		3
Bleomycin	5		3		3		3		3		3		3
Etoposide	60 ɜ 2			3				3				3	
Prednisone	40	Every other day for 10 weeks, then taper weeks 11 to 12											

more myelotoxic than ABVD but less than MEC, which required more dose reductions. CR rates for ABVD, Stanford V, and MEC were 89%, 76% and 94%, respectively. FFS and PFS of ABVD and MEC were superior to Stanford V when given limited and conditioned radiotherapy; therefore, ABVD remained the optimal treatment therapy when combined with optional and limited rather than adjuvant or consolidative radiotherapy. It is important to note, however, that the Stanford V protocol delivered in Europe was not identical to that developed at Stanford, which may explain its apparent reduced efficacy as reported in this study. A recently completed phase III study comparing ABVD and Stanford V in 855 previously untreated patients with advanced HL (ECOG/Southwest Oncology Group [SWOG] 2496/CALGB 59905) is undergoing analysis and the data are expected to be reported in 2010.

Finally, in an abstract presented at the 2008 American Society of Clinical Oncology (ASCO) meeting, Gianni and colleagues described the results of their study comparing 8 cycles of ABVD with 4 of escalated BEACOPP followed by 4 of standard BEACOPP.[17] Even though the 3-year FFP favored BEACOPP, there was no difference in survival (91% for ABVD, 90% for BEACOPP).

Therapy for NLP HL

The therapy for patients with NLP HL is controversial. Only 5–20% present in advanced stages. A "watch and wait" approach has been recommended by some for patients with limited stage disease, although radiotherapy is more often used. In the German Hodgkin Study Group (GHSG) trial of patients with early-stage disease, an OS of 99% and FFS of 95% were reported in patients treated primarily with radiotherapy.[18] Advanced-stage disease can be managed very effectively with treatment paradigms used for cHL (ie, chemotherapy, combination chemotherapy or biotherapy [rituximab]), with comparable results. Several phase II studies have suggested response rates approaching 80% using rituximab as a single agent.[19] The role of this antibody as part of an initial treatment approach remains to be determined.

Treatment of Relapsed/Refractory HL

In patients with relapsed/refractory cHL, patient-related features such as age, performance status, organ function, and the type of and response to previous therapy need to be taken into account when considering further treatment options. Moskowitz and colleagues from the Memorial Sloan-Kettering Cancer Center reported their data for ifosfamide, carboplatin, and etoposide (ICE) followed by autologous stem cell transplantation (ASCT) for relapsed/refractory disease.[20] In this study, 65 patients—22 with primary refractory HL and 43 with relapsed HL—were treated with 2 biweekly cycles of ICE. Peripheral blood progenitor cells from responding patients were collected, and patients were given acceler-

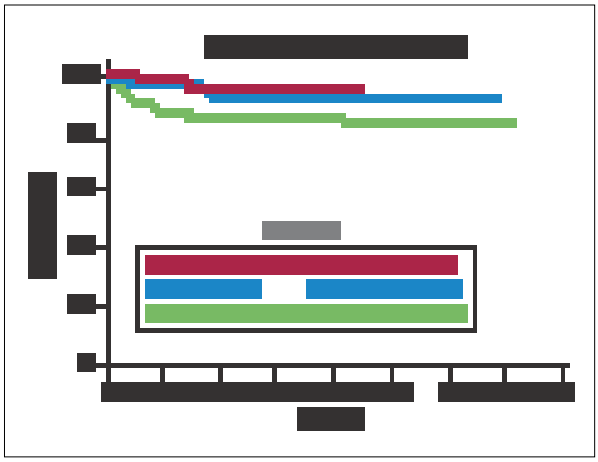

Figure 2. Stanford V plus radiotherapy for Hodgkin lymphoma.

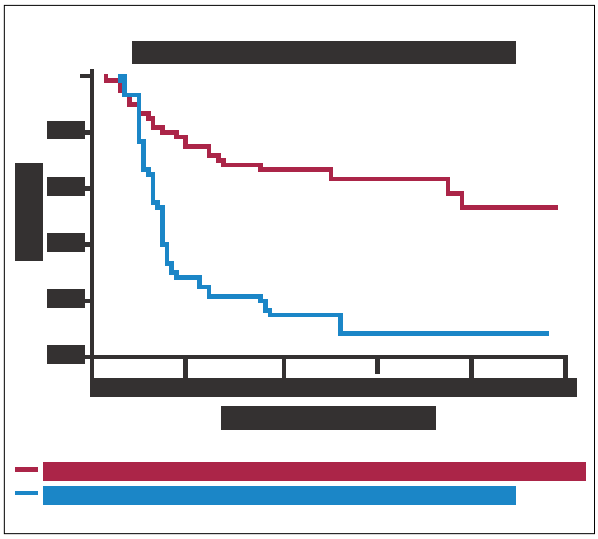

Figure 3. Event-free survival with GVD (gemcitabine, vinorelbine, and liposomal doxorubicin) plus autologous stem cell transplant and GVD after failing prior transplant.

Data adapted from Bartlett NL. *Ann Oncol.* 2007;18:1071-1079.

ated fractionation IFRT followed by cyclophosphamide-etoposide and either intensive accelerated fractionation total lymphoid irradiation or carmustine and ASCT. The EFS rate at a median follow-up of 43 months was 58%, and the response rate to ICE was 88%. The EFS rate for patients posttransplant was 68%. These data demonstrated the effectiveness of dose-dense and dose-intense cytoreductive chemotherapy followed by ASCT in relapsed/refractory disease.

For patients who are not candidates or who have progressed following stem cell transplantation, alternative approaches may include single agents and novel drugs (eg, gemcitabine, anti-CD30 antibodies, SGN-35, rituximab, and histone deacetylase [HDAC] inhibitors). Single-agent gemcitabine has been associated with reported response rates of 20–60% with some CR, but with a duration of response generally approximately 6–9 months.[21] The CALGB developed a GVD regimen (ie, gemcitabine, vinorelbine, and liposomal doxorubicin) which has been evaluated in a study of 91 patients. Reported response rates were 61% for transplant-naive patients and 75% for patients with a history of stem cell transplantation (Figure 3).[22] The 4-year EFS for the transplant-naive and prior transplant groups were 70% and 52%, respectively. This regimen should now be considered a standard treatment option for relapsed/refractory HL.

Numerous studies have now confirmed ABVD as the standard of care for most patients with previously untreated HL. It is at least as effective as other regimens and is less toxic. However, we still need to improve on this current standard. Studies are evaluating the possibility of eliminating bleomycin to reduce toxicity, whereas others are attempting to incorporate newer agents to improve efficacy. To further improve the outcome of patients with HL, risk-adapted approaches are being tested and new agents are in development for patients with relapsed/refractory disease.

Improvement of Chemotherapy Regimens Beyond ABVD

Volker Diehl, MD, Professor of Medicine, University of Cologne, Cologne, Germany, reviewed how chemotherapy regimens developed beyond ABVD and presented state-of-the-art treatment options for HL.

HL is one of the success stories of modern hematology/oncology, with cure rates of 80–90% in all stages. Unfortunately, 30% of patients with advanced-stage disease progress or relapse, and there is a 5–15% late morbidity and mortality rate due to chemotherapy and radiation or combinations of the 2.[23] Moreover, the fact that several of the active drugs are carcinogens or co-carcinogens has led to the induction of secondary neoplasias (eg, by cyclophosphamide, procarbazine, and etoposide); also, there is cardiopulmonary toxicity from doxorubicin and bleomycin. ABVD should not be considered an easy option for younger patients because of long-term doxorubicin- and vincristine-induced toxicities, which may persist for several years after ABVD, even without radiotherapy. Finally, there is currently no satisfactory risk adaptation of therapy such that some patients are overtreated while others may be undertreated.

Thus, a number of clinical problems should be addressed. Important considerations include whether ABVD is the correct standard of care, and, if so, what options are available for patients who are refractory or who relapse? Is high-dose therapy with stem cell transplantation the only answer? How can we identify, at diagnosis, the good- or bad- prognosis patients? Is it better to use early intensification versus later dose intensity? Should therapy be tailored on the basis of the International Prognostic Score (IPS; risk adaptation) or can FDG-PET be used to discriminate between a good and a bad treatment response with a subsequent alteration in therapy (response adaptation)?

Beyond ABVD: Fourth-generation Regimens

For certain risk groups of patients with advanced-stage disease, ABVD should not be considered a gold standard because of those patients' poor outcome with this regimen. Thus, one size does not fit all. This problem has led to the development of a number of fourth-generation

Table 3. Efficacy of ABVD Compared With BEACOPP in Trials of Advanced-Stage Hodgkin Lymphoma

Source	Chemotherapy	5-Year Failure-Free Survival, %	5-Year Overall Survival, %
Canellos[10]	6–8 ABVD	61	73
	6 (MOPP+ABVD)	65	75
Duggan[12]	8–10 ABVD	63	82
	8–10 MOPP/ABV	66	81
GHSG HD*	4 (COPP+ABVD)	68	83
	8 BEACOPP esc.	68	92

*Data provided by R. Naumann, MD.

ABVD=doxorubicin, bleomycin, vinblastine, dacarbazine; BEACOPP=bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; GHSG=German Hodgkin Study Group; MOPP=mechlorethamine, vincristine, procarbazine, prednisone

regimens including Stanford V, COPP/EBV/CAD (MEC), BEACOPP, BEACOPP-D (BEACOPP with etoposide removed), and ABVD plus rituximab. Each of these regimens could potentially challenge ABVD as the standard of care for advanced HL in this population. The question is whether there are ample comparative data to demonstrate superiority of one regimen over the others. Neither the Stanford V nor the MEC regimen has yet demonstrated clear superiority over ABVD. The question of whether Stanford V or ABVD is superior will not be answered until the results of a large phase III study comparing ABVD and Stanford V (ECOG 2496/CALGB 59905) are available.

There is now extensive clinical experience with BEACOPP. More than 2,000 patients have been treated in 3 randomized prospective trials throughout Europe, with more than 10 years of follow-up available for the escalated regimen (Table 3).[7,14] A recent update of the HD9 trial from the GHSG compared baseline and escalated BEACOPP with COPP alternating with ABVD in 1196 patients with advanced-stage disease.[24] Patients were randomized to 8 cycles of COPP, 8 cycles of standard-dose BEACOPP, or 8 cycles of escalated-dose BEACOPP. With a median follow-up of 112 months, dose-escalated BEACOPP produced a 10-year OS rate of 86%; that of standard BEACOPP was 80%, and that of COPP-ABVD regimen was 75%. Escalated BEACOPP had a significantly improved 10-year OS rate compared to standard BEACOPP (P=.0053) and to COPP-ABVD (P<.001). The 10-year freedom from treatment failure (FFTF) analysis showed correspondingly similar data: 82% for escalated BEACOPP versus 70% for standard BEACOPP (P<.0001) and 64% for COPP-ABVD (P<.001). The HL-related death rate at 10 years was 11.5% for COPP-ABVD versus 8.1% and 2.8% for standard and escalated BEACOPP, respectively. The advantage for escalated BEACOPP held for all IPS risk groups. All the other causes of death were similar among groups. The overall secondary malignancy rates were 3.6% and 3.2% for baseline and escalated BEACOPP, respectively, and 3.1% for the COPP-ABVD regimen. Although the higher rate of secondary AML after escalated BEACOPP may have been a chance occurrence, the authors noted that 70% of patients in this group had additional radiotherapy. These data demonstrate a significant improvement in long-term disease control for advanced-stage HL, although a formal comparison of BEACOPP and standard-dose ABVD will be necessary to supplant ABVD as standard of care for this patient population.

Gianni and colleagues reported a preliminary analysis of a comparison of ABVD versus escalated BEACOPP in 321 patients with advanced-stage disease (ie, stages IIB to IV).[17] Patients received 6–8 cycles of ABVD or 4 cycles of dose-escalated BEACOPP plus 4 of baseline BEACOPP with radiotherapy. Patients failing to respond proceeded to ASCT following BEAM (carmustine, etoposide, cytarabine, and melphalan). At 3 years, OS was 91% and 90% for the ABVD and BEACOPP arms, respectively. Freedom from second progression was 87% and 92% for the ABVD and BEACOPP arms, and there was no significant difference in 3-year FFP.

A number of attempts have been made to maintain the efficacy of escalated BEACOPP while reducing its toxicities. The GHSG compared its updated experience with escalated BEACOPP with a BEACOPP-14 regimen (baseline BEACOPP delivered every 14 days) in more than 2,000 patients. At 10 years, the overall CR rate was over 90%; less than 15% of patients required radiation. FFTF was 82–88% with an OS of 86–90%. The risk of MDS/AML was 0.9%. Furthermore, Naumann and colleagues used a modified version of BEACOPP, called BACOPP-D, in which the etoposide is removed to reduce leukemogenicity.[25] The results to date, according to a personal communication with Dr. Naumann, show that at 36 months, OS is 92% (95% CI, 0.841–0.962) with an 88% PFS. The toxicity of the regimen was considered less than that of escalated BEACOPP or BEACOPP-14.

Biotherapy in the Microenvironment of HL

As the malignant cell in HL—the Reed-Sternberg cell—comprises a very small portion of the tumor, it is likely that there is an important role for the microenvironment in maintaining tumor growth (Figure 4). Younes and col-

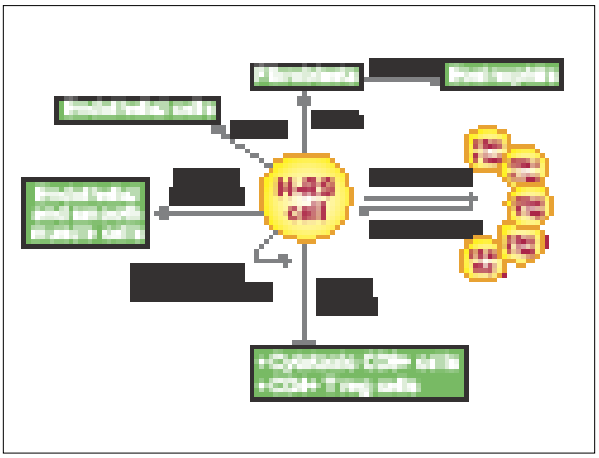

Figure 4. The HL tumor cell and its microenvironment.

IL=interleukin; TARC=thymus and activation regulated chemokine; TGF=transforming growth factor; TNF=tumor necrosis factor; VEGF=vascular endothelial growth factor.

leagues conducted a study in which rituximab and ABVD were given together to patients with newly diagnosed cHL.[26] The rationale for this approach was threefold. First, Reed-Sternberg cells do not survive outside their microenvironment, which largely contains B cells; therefore, depleting B cells from that microenvironment with anti-CD20+ therapy should facilitate the efficacy of chemotherapy. Second, there have been data suggesting that Reed-Sternberg stem cells are CD20+. Third, rituximab may have a direct killing effect on CD20-expressing Reed-Sternberg cells.[26] In this study, rituximab was given at the standard dose of 375 mg/m^2 weekly for 6 weeks, either concurrently with ABVD or beginning 3 weeks before the initial dose of chemotherapy. The effect of the combined therapy on FDG-PET imaging after 2–3 cycles of ABVD was evaluated to determine whether FDG-avidity could predict treatment outcome in patients receiving ABVD and rituximab. In 59 evaluable patients, those who remained FDG-PET–positive had an inferior EFS compared to those who were FDG-PET–negative. The difference was significantly better than what has been reported with standard ABVD. Five-year EFS for patients with a negative FDG-PET scan was 93%, compared with 75% for those who remained FDG-PET–positive (*P*=.005). However, there was no difference in EFS between FDG-PET–positive and –negative patients after 2–3 cycles of chemotherapy if they had an IPS of 0–2. The difference with IPS 3–7 also did not reach significance because of small numbers. A randomized trial comparing ABVD with or without rituximab is planned to confirm these observations.

Prognostic Indicators of Disease Progression

Identification of poor prognosis patients remains a challenge, as 30–35% of patients experience progression or are resistant to initial therapy. One factor that may contribute to patient outcome is an interaction between HL tumor cells and their microenvironment. Identification of patients who would benefit from early dose intensification (ie, high-risk patients) may rely on a balance between IPS and the extent to which the microenvironment can be successfully manipulated. Gene expression analysis is beginning to identify genes associated with outcome on signature including genes related to host immune response and tumor microenvironment (STAT1) and another of cell cycle (CDC2), but at present this procedure is not available for general use.[27]

A key question is how powerful FDG-PET is as a predictive test, compared with traditional schemes such as the IPS. In addition, how can this information be used successfully for risk-directed therapy. Gallamini and colleagues evaluated the prognostic role of early FDG-PET and IPS in 260 newly diagnosed patients with HL presenting with advanced disease (n=190, stages IIB–IVB) or with stage IIA disease and adverse prognostic factors.[28] All but 11 patients were treated with conventional ABVD, followed by consolidation radiotherapy (bulky presentation or residual tumor mass). Conventional radiological staging and an FDG-PET scan were performed at baseline; FDG-PET scan was repeated after 2 courses of ABVD with no treatment alteration permitted on the basis of the second scan (FDG-PET-2). At median follow-up of 2.19 years, (range, 0.32–5.18 years), 205 patients were in continuous complete remission (CCR), 2 patients were in partial remission, 43 had progressed, and 10 had relapsed (Figure 5). The 2-year PFS for patients with positive FDG-PET-2 results was 12.8%; 2-year PFS for patients with negative FDG-PET-2 results was 95% (*P*<.0001). In a univariate analysis, treatment outcome was significantly associated with FDG-PET-2 (*P*<.0001), stage IV (*P*<.0001), white blood cell count more than 15,000 µL (*P*<.0001), lymphopenia (*P*<.001), IPS as a continuous variable (*P*<.0001), extranodal involvement (*P*<.0001), and bulky disease (*P*=.012). In multivariate analyses, only FDG-PET-2 turned out to be significant (*P*<.0001). Thus, the second FDG-PET scan was more prognostic than IPS and was potentially the optimal tool to plan risk-adapted treatment in advanced HL.

The role of early intensification as a means of overcoming resistance has been studied in an Italian/French study in which patients received 4 doses of ABVD and were then randomized to 4 additional cycles or to high dose therapy with stem cell support. There was no difference in outcome, which might be attributed to the delay in intensification since 20% of failures occurred prior to

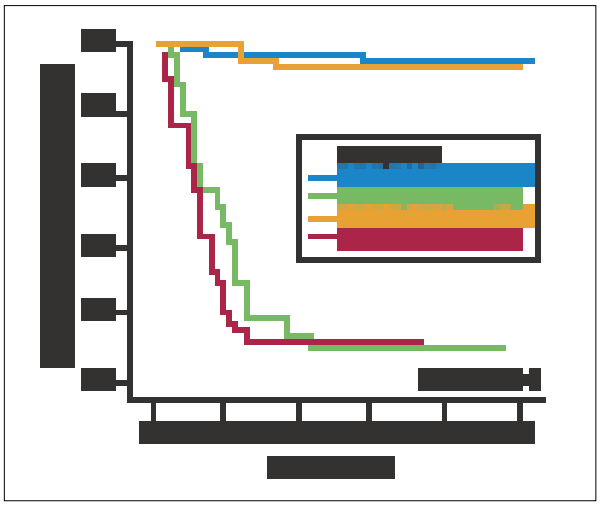

Figure 5. The ability of positron emission tomography imaging and the IPS score to predict outcome in Hodgkin lymphoma.

IPS=International prognostic score.

Data adapted from Gallamini A et al. *J Clin Oncol*. 2007;25:3746-3752.

that time.[29] Such observations suggest the possibility, now under study, that early intensification is needed for high-risk patients, with de-escalation if the FDG-PET scan becomes negative after the first 2–3 cycles. In the future GSHG HD18 study for advanced-stage disease, patients will receive 2 cycles of escalated BEACOPP. Those who remain FDG-PET–positive will be randomized to 2 escalated and 4 baseline BEACOPP regimens with or without rituximab.[30] Those who still remain positive will undergo radiotherapy. Those who become FDG-PET–negative after 2 escalated BEACOPP regimens will be randomized to 2 escalated BEACOPP regimens followed by 4 baseline BEACOPP or 2 escalated BEACOPP regimens without radiation. This concept is also being tested by the UK/Nordic Group and an Israeli group.

Dr. Diehl concluded that patients with advanced HL should still be treated on a clinical trial. Possible future strategies include risk-adapted therapy using FDG-PET, early intensification, and incorporating new agents such as lenalidomide, bevacizumab, mammalian target of rapamycin (mTOR) inhibitors, and monoclonal antibodies directed against antigens such as CD30.

Novel Treatments for Hodgkin Lymphoma

Anas Younes, MD, Professor, The University of Texas M. D. Anderson Cancer Center, Houston, reviewed pathways and cellular entities in HL that are being actively pursued as therapeutic targets. He focused on novel treatments that target the cancer cells either directly via cellular surface receptors or indirectly via survival pathways.

HL has a very characteristic expression of multiple cytokines, accounting not only for its unique clinicopathologic features but also the opportunities for therapeutic intervention that it provides. The Reed-Sternberg cells that characterize HL are surrounded by an overwhelming number of reactive inflammatory cells: B lymphocytes, T lymphocytes, monocytes, and other cells expressing receptors that can be targeted by monoclonal antibodies. In addition, several known cellular survival pathways present potential targets for small molecules (Figure 6).[2]

Antibody-based Therapeutics in HL

HL is a model disease for anti-CD30 antibodies due to the expression of that antigen on Reed-Sternberg cells.

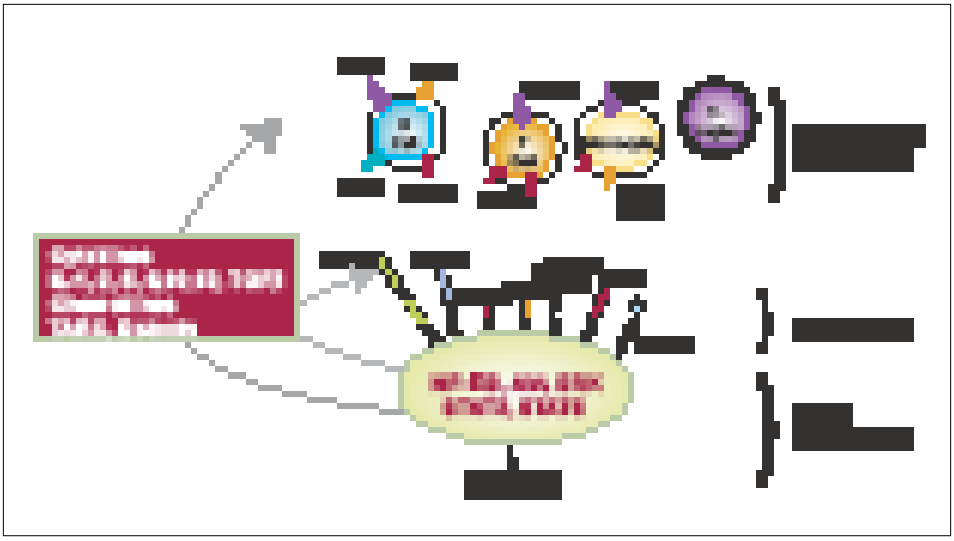

Figure 6. Intracellular targets in Reed-Sternberg cells and their microenvironment.

However, the first generation anti-CD30 antibodies (eg, SGN-30 and MDX-060) proved to be disappointing in terms of clinical responses in patients with relapsed HL. More encouraging results have been achieved with SGN-35, which uses the same backbone as SGN-30 but is conjugated to monomethyl auristatin E (MMAE). It binds to CD30, leading to the internalization of the antibody-drug-conjugate, MMAE release, and the subsequent binding to tubulin, which ultimately prompts cell cycle arrest and apoptosis.[31] A multicenter, phase I, dose-escalation study was conducted in patients with refractory or recurrent CD30-positive hematologic malignancies; this was done to define the safety and maximum tolerated dose of SGN-35 administered at dose levels of 0.1–1 ng/kg every 21 days.[32] Secondary study objectives included determining the pharmacokinetic profile, antitumor activity, and immunogenicity of the therapy. Of 39 heavily pretreated patients, 36 had HL, 2 had systemic anaplastic large-cell lymphoma, and 1 had angioimmunoblastic T cell lymphoma; 29 patients (74%) had previously undergone ASCT. SGN-35 was well tolerated at all dose levels and produced clinical benefit at doses at or above 1.2 mg/kg in 19 patients (86%). An objective response was observed in 10 patients (45%). CR, as assessed by the revised response criteria, was observed in 5 patients (23%).[33] The study is ongoing to determine the maximum tolerated dose, and a weekly dosing regimen is also being studied.

Kapp and colleagues demonstrated that interleukin 13 (IL-13) secreted by Reed-Sternberg cells stimulates their growth and that blocking this cytokine leads to cellular inhibition and decreased proliferation.[35] Antibodies to IL-13 itself rather than cellular receptors of the cytokine decreased cellular proliferation with potential clinical sequelae. The University of Texas M. D. Anderson and Memorial Sloan-Kettering Cancer Centers are collaboratively investigating TNX650, a fully human antibody to IL-13 that can be a potential therapy for HL. The phase I/II, multidose, dose-escalation study in patients with relapsed/refractory HL is completed and is expected to be reported in early 2009.

Small Molecules in HL

Several small molecules are also being evaluated in HL. The use of bortezomib in HL is based on strong preclinical rationale. Constitutive activation of nuclear factor-κB (NF-κB) has been described in patient-derived Reed-Sternberg cells and HL cell lines and contributes to the proliferation and survival of HL.[35] Inhibition of the proteasome with bortezomib may inhibit overexpression of NF-κB by preventing degradation of IκB, which sequesters NF-κB in the cytoplasm.[35] However, when clinically evaluated by 3 independent groups, there was no meaningful single agent activity in heavily pretreated patients with relapsed classic disease who underwent the dose and schedule that is effective for multiple myeloma.[36-38] Despite these disappointing initial results, bortezomib continues to be studied in HL in combination with other therapies, based on the suggestion that proteasome inhibition modulates the sensitivity of intracellular processes to other drugs. Younes and colleagues are actively studying bortezomib with ICE chemotherapy at first relapse of cHL, with patients being randomized to ICE or bortezomib plus ICE.

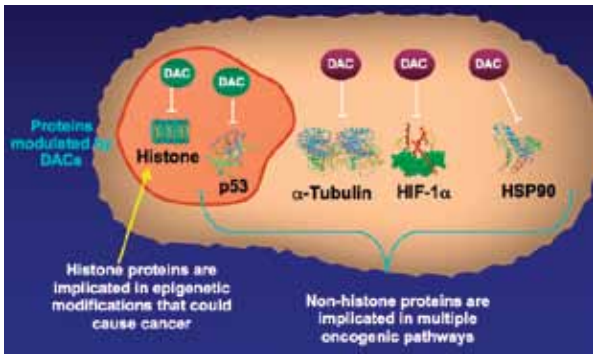

Figure 7. The implication of DACs in malignant disease by modulation of histone and nonhistone proteins in oncogenesis.

DAC=deacetylase; HIF=hypoxia inducible factor.

The heat shock protein HSP-90 is one of the most common heat shock proteins and plays a vital role in protein folding, cell signaling, and tumor repression. In the HL microenvironment, HSP-90 maintains cell survival by interacting with multiple cellular transcription factors. Thus, inhibition of HSP-90 leads to the inhibition of multiple survival pathways, producing potentially synergistic effects; 17-allylamino-17-demethoxygeldanamycin has been developed as a small-molecule inhibitor of HSP-90.[39]

The Role of Epigenetics in the Growth and Survival of HL

Epigenetics, the process of heritable alterations in gene expression, not related to changes in DNA sequence, is emerging as another potential therapeutic target in HL. The Reed-Sternberg cell is of B-cell origin, but the B-cell phenotype is lost when B-cell genes are epigenetically silenced as the cell matures. This process can be reversed in Hodgkin cell lines by hypomethylating agents (eg, decitabine), which have been shown to reactivate B-lineage genes and induce the expression of CD19 and CD20.[40]

Deacetylase (DAC) inhibition represents another epigenetic pathway. Human DACs are classified into 2 major families: zinc dependent and nicotinamide adenine dinucleotide (NAD)+ dependent. The former is further classified as class I, II, and IV. DACs act on many intracellular proteins including histone and nonhistone proteins (eg, alpha tubulin, HSP-90; Figure 7). Vorinostat

Table 4. Clinical Response to the HDAC Inhibitor MGCD-0103 in Patients With Relapsed/Refractory Hodgkin Lymphoma

	Patients, N	Rates, %	
Objective Response	110 mg Cohort	Total Enrolled (n=23)	Total Evaluable (n=21)
CR	2	9	10
PR	6	26	29
SD ≥6 cycles	–	–	–
CR + PR (≥50% tumor reduction)	8	35	38
Objective Response	85 mg cohort	Total enrolled (n=15)	Total evaluable (n=8)
CR	–	–	–
PR	2	13	25
SD ≥6 cycles	1	7	13
CR + PR (≥50% tumor reduction)	2	13	25
R + PR + SD (≥6 cycles)	3	20	38

CR=complete response; PR=partial response; R=response; SD=stable disease

Data adapted from Younes A et al. *Ann Oncol.* 2008;19(suppl 4): Abstract 137.

is the only HDAC inhibitor approved in the United States and is licensed for use in cutaneous T-cell lymphoma.[41]

MGCD0103 is an oral, isotype-selective HDAC inhibitor with demonstrated antitumor activity in a variety of cancers.[42] It is being evaluated in a multicenter phase II trial in patients with relapsed/refractory disease, 82% of whom have received prior transplant therapy; 4 patients (13%) had both autologous and allogeneic transplants.[43] The study objectives were 1) to assess the safety and efficacy of MGCD0103 and 2) to evaluate potential biomarkers/predictive markers for efficacy (eg, plasma levels of thymus and activation regulated chemokine [TARC] being determined by enzyme-linked immunosorbent assay [ELISA]). MGCD0103 inhibits STAT6 in the HL cell lines and STAT6 induces TARC secretion.

To date, 38 patients who received either 110 mg (n=23) or 85 mg (n=15) of MGCD0103 thrice weekly in 4-week cycles have been enrolled. Of 20 evaluable patients treated with the 110 mg dose, 2 (9%) achieved CR and 6 (26%) PR (ORR, 35%). Computed tomography (CT) data showed that 12 patients (60%) had a 25% or higher decrease in tumor size; 85% overall had some tumor reduction. Among the 15 patients enrolled at a starting dose of 85 mg, 2 (13%) attained PR, and 1 (7%) had stable disease (SD) for 6 or more cycles; overall disease control rate (CR plus PR plus SD) in this group was 20%. Preliminary data from the 10 patients in the 85 mg cohort evaluable for efficacy showed that 7 (70%) experienced a 25% or higher decrease (Table 4). There were fewer serious drug-related adverse events at the 85 mg dose. The most commonly reported hematologic adverse event was thrombocytopenia at both starting doses (17% at 85 mg and 20% at 110 mg). Four patients (17%) discontinued the study because of an adverse event at the 110-mg starting dose compared to 3 (20%) at the 85-mg dose. The median duration of therapy for responders was 6.1 cycles (range, 3–12); the median time to response in this group was 2.2 cycles (range, 1–4.4). The median duration of therapy for all enrolled patients was 4 cycles (range, 1–12). Interestingly, plasma TARC levels correlated with tumor shrinkage, indicating a potential role of this cytokine as a future surrogate marker for the efficacy of HDAC inhibitors.

An alternative pathway in HL that is under evaluation includes mTOR, a serine/threonine protein kinase that regulates cell growth, proliferation, motility and survival, protein synthesis, and transcription.[44] Johnston and colleagues reported promising single agent activity with everolimus in a small study in patients with relapsed/refractory disease.[45] A total of 17 patients with HL were treated with 10 mg daily for each 28-day cycle (up to 12 mg, with a possible extension in responders) and restaged after 2, 6, and 12 cycles. The primary endpoint was the confirmed response rate, including CR, unconfirmed CR, or PR. Fifteen patients were evaluable for response, and the ORR was 47% (7/15)—all PRs. Ten patients were reported as continuing the study; 6 discontinued therapy because of disease progression, and 1 for other reasons. It was concluded that everolimus shows promising activity with an acceptable toxicity profile and warrants further

evaluation in HL, specifically in regimens for relapsed/refractory disease.

Risk-directed Therapy (FDG-PET)

John Radford, MD, Professor of Medicine and Oncology, Christie Hospital and the University of Manchester, Manchester, United Kingdom, discussed the latest viewpoint on risk-directed therapy and how to best integrate FDG-PET into the management of HL. This discussion included a review of the key issues unique to HL, namely the relatively young age of patients, and high cure rate with late effects of treatment that make optimization of individual treatment critical in this disease.

HL has a very high cure rate with an expected long-term survival for most patients, the majority of whom are young. Consequently, the late effects of treatment on fertility and cardiovascular disease are highly relevant to this population of patients. Death from HL is a main concern in the first 10 years following diagnosis; however, beyond that time, secondary malignancies and cardiovascular disease become major problems (Figure 8).[46] Thus, the goal of therapy should be to optimize individual treatment, maximize cure, and minimize toxicity. So-called risk-directed therapy is highly relevant for patients with HL (ie, identifying patients who, from the outset, will have a better or worse outcome and integrating response adaptation).

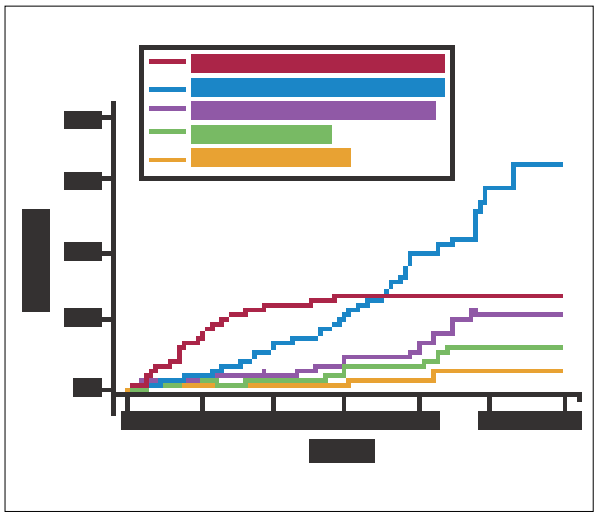

Figure 8. Competing causes of death in patients with Hodgkin lymphoma

Data adapted from Ng et al. *J Clin Oncol.* 2002;20:2101-2108.

Potential Role of FDG-PET in HL: Issues and Applications

FDG-PET has a potential role in HL in 4 distinct areas: staging, during therapy, restaging after chemotherapy, and in follow-up. FDG-PET could be utilized after 1 or more cycles of chemotherapy to determine suitability for dose escalation or de-escalation, the need for consolidation radiotherapy, and the suitability for high-dose chemotherapy (response-adapted therapy). However, FDG-PET is a relatively new technology, and caution is warranted before its widescale application in response-adaptive therapy.

The imaging subcommittee of the International Harmonization Project for FDG-PET has defined FDG-PET positivity in 2 ways that take the size of lesions into account.[47] First, for masses 2 cm or more in diameter, a positive reading is defined as FDG activity greater than the mediastinal blood pool. For smaller lesions (1.1–1.9 cm), FDG activity greater than the surrounding background implies positivity. However, false positives may arise from a variety of causes such as infection, granulomatous disease (eg, sarcoidosis), the presence of brown fat, and procedural errors such as scanning beyond the resolution of the technology or scanning too soon after treatment. Optimal times for FDG-PET scans have been identified as 6–8 weeks after chemotherapy and 8–12 weeks following radiotherapy. False negatives can also occur in hypoglycemic patients and in certain histologies (eg, marginal zone lymphoma, T-cell lymphoma) where FDG avidity is in the range of approximately 40–50%. FDG-PET is thus an inexact science.

FDG-PET in Staging HL

The concordance of CT scanning and FDG-PET in staging of HL is in the range of 60–80%, which is lower than that of other lymphomas such as diffuse large B-cell lymphoma, follicular lymphoma, and mantle cell lymphoma. There is also a higher sensitivity and false positive rate in HL compared to NHL. Detection of bone marrow involvement by FDG-PET in HL is unreliable; thus, bone marrow trephines continue to be required.[48] Various studies have shown that despite the increased sensitivity of FDG-PET relative to CT scans, few stage and treatment changes occur as a result.[48,49] The value of FDG-PET may be less as a staging tool, but better for comparison with subsequent posttherapy images. Unenhanced FDG-PET/CT is more sensitive and specific than IV contrast full-dose CT alone or FDG-PET alone in terms of nodal and extranodal detection of disease; FDG-PET CT sensitivity is 88% versus 50% for CT alone, and the specificity is 100% versus 90%, respectively.[50] However, there is no difference between unenhanced low-dose FDG-PET/CT and IV contrast–enhanced full-dose FDG-PET/CT.[51]

Overall, IV contrast–enhanced low-dose FDG-PET/CT is a reasonable choice for a single imaging modality.

FDG-PET Response-Adapted Therapy

Questions to be considered for response-adapted therapy include 1) whether FDG-PET can identify patients who may benefit from consolidation radiotherapy; 2) whether FDG-PET can identify those patients who might benefit from treatment escalation and those for whom de-escalation should be considered; and 3) whether FDG-PET can predict outcome before high-dose chemotherapy for recurrent disease.

An ongoing study in the United Kingdom addresses whether a negative FDG-PET scan after chemotherapy is a valid biomarker of disease control to the extent that radiotherapy can subsequently be avoided without a potentially negative effect on patient outcome.[52] The UK National Cancer Research Institute FDG-PET Scan Trial is accruing patients with stage IA and IIA disease. Patients receive 3 cycles of ABVD. If there is no response or progressive disease at reassessment, patients go off study and are treated in a salvage setting. If they achieve a CR or PR as measured by conventional criteria, they undergo FDG-PET scanning. If the FDG-PET scan is positive and indicative of residual disease, patients receive a fourth cycle of ABVD followed by IFRT. If the FDG-PET scan is negative, patients are randomized to receive either IFRT or no further treatment. A total of 320 patients will be randomized to the negative FDG-PET arm. The risk of reducing disease control is mitigated by the fact that recurrent disease in patients who are not irradiated first-line may be successfully treated by subsequent salvage radiotherapy. In addition, reducing the number of patients exposed to radiotherapy may produce a greater overall survival benefit because of less secondary malignancies and reduced cardiovascular disease. To achieve consistency, regional FDG-PET centers were established and calibrated using standard phantoms, and data are transferred electronically to a core laboratory for central review.[52]

At the time of the first interim analysis, 258 patients were enrolled (131 male, 127 female; median age, 34.5 years). Of the 216 patients who received FDG-PET scanning, 81% had a positivity score of 1 or 2 (negative), and 19% had a score of 3, 4 ,or 5, yielding an FDG-PET positivity rate of 19%. Of the FDG-PET negative patients, 171 were randomized to receive either IFRT or no further treatment. Once they were informed that their FDG-PET scan was negative, 4 patients chose not to be randomized. At a median follow-up of 6 months, 166 of 177 were alive and progression-free, 3 had progressed, and 2 patients died—1 from HL and 1 from treatment. Conclusions to date are that trials involving a randomized question after Central Review of FDG-PET are feasible. An FDG-PET positivity rate of 19% is at the upper end of the expected range. The event rate after short follow-up is very low, and recruitment continues.[52]

Gallamini and colleagues demonstrated that early clearance of FDG-PET is a strong predictor of outcome (Figure 5).[53] Taking the risk-adapted approach, it is clear that after 2 cycles of treatment, FDG-PET negativity confers a better prognosis than does persistent FDG-PET avidity, which holds true irrespective of IPS score. The RATHL trial will attempt to confirm this observation in patients who undergo baseline FDG-PET followed by 2 cycles of ABVD, followed by a second FDG-PET scan.[54] If the scan is negative, patients will be randomized to either 4 cycles of AVD (bleomycin is the drug of choice for omission because of its adverse pulmonary effects and questionable activity) or continuing ABVD. If the scan is positive, treatment escalation using BEACOPP is planned to determine the possibility of overcoming disease resistance at that point (Figure 9).

A number of studies have shown that residual FDG-avidity in patients who relapsed and received salvage chemotherapy prior to high-dose chemotherapy show a high risk of relapse and a poor prognosis.[55]

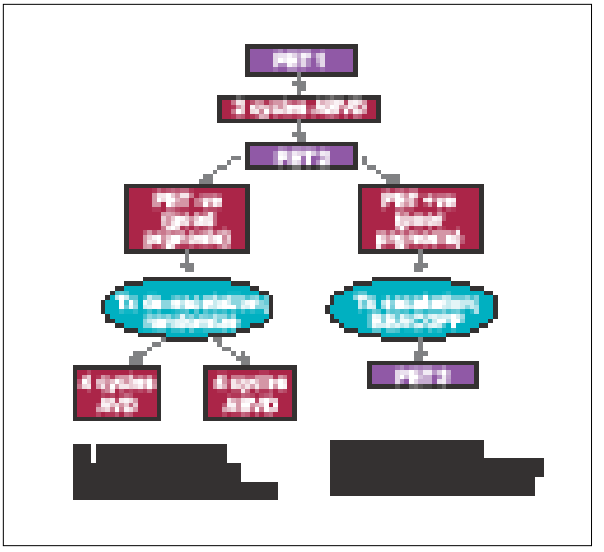

Figure 9. The RATHL trial: a randomized phase III trial to assess response-adapted therapy using FDG-PET imaging in patients with newly diagnosed, advanced Hodgkin lymphoma.

ABVD=doxorubicin, bleomycin, vinblastine, dacarbazine; BEACOPP=bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; PET=positron emission tomography; Tx=treatment.

FDG-PET in Follow-up

Relapse is identified more than 80% of the time as a result of symptom-prompted investigation, which raises the question of whether early detection confers benefit. If there is no benefit, there is little to be gained from the procedure, especially as there may be a negative impact—on patient psychologic health from the intense surveillance and on physical well-being from exposure to CT scan of FDG-PET scan–induced radiation. Jerusalem and colleagues performed FDG-PET scans every 4–6 months in 36 patients with HL.[56] Relapse was detected in 4 patients, 2 of whom had symptoms, and produced 6 false positives. Therefore, routine use is currently unjustified but further evaluation in clinical trials is appropriate.

In summary, PET alone cannot replace CT alone; IV contrast low-dose PET/CT may be the preferred single imaging modality. Studies of response-adapted therapy are important to identify patients suitable for dose escalation or de-escalation, those requiring radiation, and those unlikely to benefit from high-dose therapy with stem cell transplantation. Finally, FDG-PET as part of patient follow-up is of unproven benefit and should be performed only in the context of a clinical trial.

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Hodgkin Lymphoma: Advancing Beyond Standard Management

CME Post-Test: *Circle the correct answer for each question below.*

1. Classical HL is characterized by

   a. having more T cells than B cells
   b. having more B cells than T cells
   c. having lymphhocytic and histiocytic cells
   d. having an immunophenotype negative for CD15 and CD30

2. In the CALGB study comparing ABVD to MOPP/ABV, ABVD was supported as standard therapy for advanced disease HL due to its

   a. significantly superior CR
   b. significantly superior FFS
   c. significantly superior OR
   d. favorable toxicity profile

3. In a study conducted by Federico and colleagues to characterize the efficacy of Stanford V regimen in a multicenter setting, researchers found that

   a. Stanford V was less myelotoxic than ABVD and MEC
   b. Stanford V was more myelotoxic than ABVD and MEC
   c. Stanford V was less myelotoxic than ABVD but more than MEC
   d. Stanford V was more myelotoxic than ABVD but less than MEC

4. In relapsed/refractory HL, alternatives for patients who have progressed following stem cell transplantation are:

   a. gemcitabine
   b. rituximab
   c. HDAC inhibitors
   d. all of the above

5. Reed-Sternberg cells do not survive outside their microenvironment.

   a. True
   b. False

6. Anti-CD30 antibody SGN-35 is thought to lead to what effect?

   a. internalization of ADC
   b. release of MMAE
   c. cell cycle arrest
   d. all of the above

7. According to Kapp and colleagues, interleukin 13 secreted by Reed-Sternberg cells

   a. stimulates their growth
   b. decreases cell proliferation
   c. induces apoptosis
   d. all of the above

8. Heat shock protein HSP-90 plays a vital role in

   a. protein folding
   b. cell signaling
   c. tumor repression
   d. all of the above

9. The areas in which FDG-PET has a potential role in HL are

   a. staging
   b. during therapy
   c. restaging after chemotherapy
   d. all of the above

10. FDG-PET negativity confers a better prognosis than does persistent FDG-PET avidity.

    a. True
    b. False

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