New Treatment Algorithms in Hodgkin Lymphoma: Too Much or Too Little?

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OVERVIEW

Hodgkin lymphoma treatment continues to evolve as new means of assessing response to treatment, new appreciation of important risk factors, and more effective therapeutic agents become available. Treatment algorithms integrating functional imaging now provide the opportunity to modify therapy during its delivery, allowing adjustment of duration and intensity of chemotherapy and rationale identification of patients who may benefit from the addition of therapeutic irradiation. Novel agents, including the antibody drug conjugate brentuximab vedotin and checkpoint inhibitors such as nivolumab and pembrolizumab can improve the effectiveness of treatment while keeping toxicity within acceptable limits. Carefully designed clinical trials permit the identification of superior approaches in which efficacy is enhanced and toxicity minimized. Clinicians treating patients with Hodgkin lymphoma now have access to novel treatment approaches, which will require detailed assessment of each patient and careful discussion of the goals and risks of treatment at the time of planning primary treatment, again during delivery of that treatment as data indicating ongoing effectiveness become available, at the conclusion of initial intervention, and, when the need arises, at the time of recurrence of disease.

Patients with early-stage Hodgkin lymphoma (Ann Arbor stage I or II; ESHL) have excellent outcomes with contemporary therapy. Recognition of late effects of extended field radiotherapy and excellent outcomes with involved field radiotherapy (IFRT) in combination with chemotherapy established combined modality therapy (CMT) with 4× doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) plus 30 Gy IFRT as a gold standard with a 12-year progression-free survival (PFS) and overall survival (OS) of 94%.1-5 Outcomes vary based on the frequency of absence (favorable) or presence (unfavorable) of clinical risk factors, which differs among study groups (Table 1).6,7 Within the caveats of retrospective analyses, a recent Cochrane review, meta-analysis, and registry data suggest superior PFS and OS with CMT for ESHL compared with either radiotherapy or chemotherapy alone.8-12 Observational data suggest that IFRT may reduce the risk of secondary breast cancer.13,14 In this review, we summarize studies in the CT and PET eras, which have focused on fine-tuning standard CMT to avoid giving too much therapy for favorable patients or too little therapy for unfavorable patients.

COMBINED MODALITY THERAPY IN THE CT ERA

Randomized trials in the CT era are summarized in Table 2.15-20 For favorable risk disease, efforts by the German Hodgkin Study Group (GHSG) HD10 trial to avoid giving too much treatment established 2× ABVD plus 20 Gy IFRT as an effective regimen, with equivalent efficacy and reduced toxicity compared with 4× ABVD plus 30 Gy IFRT.17 In a recent update, results were durable with a 10-year PFS of 87% and OS of 94% and no difference in the risk of second cancers.19 Interestingly, late relapse (> 5 years) was more frequent in patients with favorable disease (15-year cumulative incidence 5.3% vs. 3.9%; p = .01) and underscores the importance of long-term follow-up.21 Attempts to reduce chemotherapy intensity by omitting bleomycin or dacarbazine from ABVD in the HD13 trial resulted in impairment of disease control, with a 4% and 12% reduction in 5-year PFS, respectively.15

The therapeutic priority for unfavorable disease has been to increase treatment efficacy, and several trials investigated incorporating escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP). The GHSG HD11 and European Organization for Research and Treatment of Cancer (EORTC) H9U trials compared 4× escalated BEACOPP plus 30 Gy IFRT to 4× ABVD plus 30 Gy IFRT and failed to show a marked difference in PFS or OS.16,18 At 10 years, results were durable, with a PFS of 83% and OS of 91% in both arms.19 The subsequent HD14 trial compared a hybrid 2 + 2 regimen
(2× escalated BEACOPP plus 2× ABVD plus 30 Gy IFRT) to 4× ABVD plus 30 Gy IFRT and demonstrated a 6.2% improvement in 5-year PFS with the 2 + 2 regimen, no difference in OS, and greater toxicity.²⁰

Patients who present with a bulky mass 10 cm or larger on CT or mediastinal mass ratio greater than 0.33 represent a specific group with unfavorable disease. A subset analysis of the U.S. intergroup E2496 study reported a 5-year PFS of 85% and OS of 96% with ABVD followed by 36 Gy IFRT.²² Within Europe, this subgroup is treated variably either on protocol or in a specific group with unfavorable disease. A subset analysis of the U.S. intergroup E2496 study reported a 5-year PFS of 85% and OS of 96% with ABVD followed by 36 Gy IFRT.²²

Within Europe, this subgroup is treated variably either on protocols for unfavorable or advanced-stage disease, making outcomes specific to this subset difficult to interpret. Recently, Memorial Sloan Kettering Cancer Center reported on the prognostic significance of a different definition of bulk using transverse and coronal plane measurements on CT imaging.²³ Using more than 7 cm in either plane as an optimal cutoff, the 4-year PFS for bulky versus nonbulky disease was 80.5% versus 94.4%, respectively (p = .004).

Concerns over late effects led to efforts to omit radiotherapy for ESHL. Only one randomized trial has compared CMT to ABVD alone in the CT era. The HD6 trial compared 4 to 6× ABVD to subtotal nodal irradiation alone (favorable) or in combination with 2× ABVD (unfavorable).²⁴ At 12 years, PFS was greater in the CMT arm (92% vs. 87%; p = .05); however, OS favored the use of ABVD alone due to fewer cardiac events and second cancers. Although this study is instructive and illustrates that PFS is not a reliable surrogate for OS in early-stage disease, the results have to be interpreted cautiously, as subtotal nodal irradiation is obsolete. Additionally, several deaths in the radiotherapy arm were due to reasons other than relapsed lymphoma or potential radiotherapy-related effects. A pooled retrospective analysis compared patients with nonbulky early-stage disease treated with ABVD alone in the H6 trial to patients with a similar risk profile treated in the GHSG HD10 and HD11 trials.²⁵ Results suggested that CMT provided better disease control than ABVD alone, especially among those not achieving a complete remission on CT imaging, and OS was similar. A subgroup analysis suggested that patients achieving a complete remission on CT after 2× ABVD might not need consolidative IFRT.

### INTERIM PET RESPONSE-ADAPTED THERAPY

Efforts over the last decade have focused on tailoring therapy according to risk using an interim PET scan.²⁶ A major objective of these trials has been to assess if radiotherapy can be omitted in interim PET-negative patients and whether intensifying therapy will improve outcomes for PET-positive patients. Key prospective trials evaluating PET response-adapted approaches are summarized in Table 3.²⁷-²⁹

In the U.K. RAPID trial, patients with stage I/IIA nonbulky disease received 3× ABVD followed by a PET scan.²⁸ PET-negative patients (Deauville 1 to 2) were randomized to 30 Gy IFRT or no further therapy, whereas PET-positive patients received an additional cycle of ABVD followed by 30 Gy IFRT. In the intention-to-treat/per-protocol analyses for CMT versus chemotherapy alone, PET-negative patients had a 3-year PFS of 94.6% versus 90.8% (HR 1.13–4.95; p = .02), respecitively, with no difference in OS. Although these results suggest that outcomes with chemotherapy alone are excellent in approximately 90% of patients, noninferiority of chemotherapy alone could not be established.

### TABLE 1. Unfavorable Risk Factors in Early-Stage Hodgkin Lymphoma by Study Group

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>NCCN</th>
<th>EORTC</th>
<th>GHSG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>—</td>
<td>≥ 50 years</td>
<td>—</td>
</tr>
<tr>
<td>ESR, B symptoms</td>
<td>&gt; 50 mm/hour</td>
<td>&gt; 50 if A, &gt; 30 if B</td>
<td>&gt; 50 if A, &gt; 30 if B</td>
</tr>
<tr>
<td>Bulky disease</td>
<td>MMR &gt; 0.33 or any site ≥ 10 cm</td>
<td>MTR &gt; 0.35</td>
<td>MMR &gt; 0.33</td>
</tr>
<tr>
<td>Nodal sites</td>
<td>&gt; 3</td>
<td>&gt; 3</td>
<td>&gt; 2</td>
</tr>
<tr>
<td>Extraneous disease</td>
<td>—</td>
<td>—</td>
<td>Any extranodal lesion</td>
</tr>
</tbody>
</table>

Abbreviations: NCCN, National Comprehensive Cancer Network; EORTC, European Organization for Research and Treatment of Cancer; GHSG, German Hodgkin Study Group; ESR, erythrocyte sedimentation rate; MMR, mediastinal mass ratio; MTR, mediastinal thoracic ratio.

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**PRACTICAL APPLICATIONS**

- **ESHL can be quite successfully treated with brief multiagent chemotherapy (ABVD for two cycles) followed by involved site radiotherapy.**
- **For ESHL, an acceptable alternative to brief chemotherapy plus planned involved site radiotherapy is brief chemotherapy (ABVD for 3–4 cycles), after which involved site radiotherapy is reserved solely for patients with persistent postchemotherapy PET scan–positive disease.**
- **For advanced-stage classic (CD30-positive) Hodgkin lymphoma, the combination of doxorubicin, vinblastine, dacarbazine, and brentuximab vedotin has emerged as a more effective primary chemotherapy than ABVD that can be delivered with acceptable toxicity.**
- **Patients with recurrent Hodgkin lymphoma despite optimal primary chemotherapy should be offered treatment with high-dose chemotherapy followed by ASCT unless they have a specific contraindication.**
- **Hodgkin lymphoma that recurs after ASCT usually cannot be cured but can be very usefully palliated with new agents such as brentuximab vedotin and the checkpoint inhibitors nivolumab and pembrolizumab.**
The EORTC/Lymphoma Study Association/Fondazione Italiana Linfomi H10 trial evaluated a response-adapted strategy after 2× ABVD. Notably, the trial used contemporary involved node radiotherapy (INRT), which requires a prechemotherapy PET scan for radiation planning and is associated with more precise contouring of involved nodes and reduced field size compared with IFRT. In the standard arm, patients received 30 Gy INRT after one to two additional cycles of ABVD depending on risk. In the experimental arm, patients with a negative PET scan (Deauville 1 to 2) received two to four additional cycles of ABVD without consolidative radiotherapy. In PET-positive patients, chemotherapy was intensified to 2× escalated BEACOPP followed by 30 Gy INRT. For PET-negative patients, the final analysis confirmed that CMT resulted in a substantial improvement in 5-year PFS by 12% in favorable risk patients (HR 15.8; 95% CI, 3.79–66.07) and 3% for unfavorable risk patients (HR 1.45; 95% CI, 0.84–2.50). For PET-positive patients, 5-year PFS was 13% greater with intensified therapy compared with standard therapy with ABVD (HR 0.42; 95% CI, 0.23–0.74; p = .002).

The Cancer and Leukemia Group B-50604 trial also evaluated an adaptive design in patients with early-stage nonbulky disease. In contrast to the latter trials, PET negativity was defined as Deauville 1 to 3. After 2× ABVD, PET-negative patients received two additional cycles of ABVD without consolidative radiotherapy, whereas PET-positive patients received 2× escalated BEACOPP plus 30 Gy IFRT. At interim analysis, 3-year PFS was 92% and 66% in PET-negative and -positive patients, respectively, suggesting that intensifying therapy to escalated BEACOPP is insufficient to rescue patients with Deauville 4 to 5.

Cumulatively, the two randomized PET-adapted trials do not seem to identify a group of patients for whom radiotherapy can be omitted without some reduction in PFS. OS is excellent, but follow-up of both studies is too short to inform long-term outcomes. Recently, radiotherapy fields have further evolved from IFRT to involved site radiotherapy (ISRT), in which the field size is restricted to the pretreatment volume of involved nodal sites. A retrospective study evaluated outcomes in patients with early-stage favorable disease treated with 2× ABVD followed by a PET scan and 20 Gy ISRT in patients with a Deauville score of 1 to 2. At a median follow-up of 45 months, outcomes were excellent, with a 4-year PFS of 93% and OS of 100%, suggesting that ISRT can replace IFRT without impacting outcomes.

The ongoing GHSG HD16 trial in favorable patients is evaluating 2× ABVD plus 20 Gy IFRT (standard arm) to a PET-guided experimental arm of 2× ABVD followed by observation (PET-negative) or 20 Gy IFRT (PET-positive). The GHSG HD17 trial is investigating the potential equivalence of IFRT and INRT. Results of these two trials are awaited.

The challenge is how does one apply these various results in day-to-day practice? Clearly all studies suggest that CMT is associated with a small but noteworthy improvement in PFS in the 3% to 12% range. Radiotherapy is appropriate

### Table 2. Trials Evaluating Combined Modality Therapy for Early-Stage Hodgkin Lymphoma in the CT Era

<table>
<thead>
<tr>
<th>Trial</th>
<th>Disease Risk</th>
<th>Patient Number</th>
<th>Chemotherapy Regimen</th>
<th>Radiotherapy Field and Dose</th>
<th>OS, %</th>
<th>PFS, %</th>
<th>PFS HR (95% CI)</th>
<th>Median Follow-up, Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>GHSG HD10</td>
<td>Favorable</td>
<td>1,190</td>
<td>4 ABVD</td>
<td>IFRT 30 Gy</td>
<td>94</td>
<td>87</td>
<td>1.0 (0.6–1.5)</td>
<td>98</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2 ABVD</td>
<td>IFRT 20 Gy</td>
<td>94</td>
<td>87</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GHSG HD11</td>
<td>Unfavorable</td>
<td>1,395</td>
<td>4 ABVD</td>
<td>IFRT 30 Gy</td>
<td>91</td>
<td>83</td>
<td>1.5 (1.1–2.2)</td>
<td>106</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4 ABVD</td>
<td>IFRT 20 Gy</td>
<td>90</td>
<td>75</td>
<td>1.1 (0.7–1.6)</td>
<td></td>
</tr>
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<td></td>
<td></td>
<td></td>
<td>4 Esc BEACOPP</td>
<td>IFRT 30 Gy</td>
<td>91</td>
<td>83</td>
<td>1.2 (0.8–1.7)</td>
<td></td>
</tr>
<tr>
<td>GHSG HD13</td>
<td>Favorable</td>
<td>1,502</td>
<td>2 ABVD</td>
<td>IFRT 30 Gy</td>
<td>94</td>
<td>98</td>
<td></td>
<td>60</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2 ABV</td>
<td>IFRT 30 Gy</td>
<td>82</td>
<td>94</td>
<td>2.0 (1.2–3.4)</td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2 AVD</td>
<td>IFRT 30 Gy</td>
<td>90</td>
<td>98</td>
<td>1.5 (1.0–2.3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2 AV</td>
<td>IFRT 30 Gy</td>
<td>79</td>
<td>98</td>
<td>2.3 (1.3–4.0)</td>
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</tr>
<tr>
<td>GHSG HD14</td>
<td>Unfavorable</td>
<td>1,528</td>
<td>4 ABVD</td>
<td>IFRT 30 Gy</td>
<td>97</td>
<td>89</td>
<td>0.5 (0.3–0.7)</td>
<td>43</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>2 Esc BEACOPP + 2 ABVD</td>
<td>IFRT 30 Gy</td>
<td>97</td>
<td>95</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EORTC H9-U</td>
<td>Unfavorable</td>
<td>808</td>
<td>4 ABV</td>
<td>IFRT 30 Gy</td>
<td>94</td>
<td>86</td>
<td></td>
<td>90</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>4 Esc BEACOPP</td>
<td>IFRT 30 Gy</td>
<td>93</td>
<td>89</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>6 ABV</td>
<td>IFRT 30 Gy</td>
<td>93</td>
<td>90</td>
<td>NR</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: Esc, escalated; NR, not reported.
NEW TREATMENT ALGORITHMS IN HODGKIN LYMPHOMA

TABLE 3. Prospective Trials Evaluating PET-Adapted Approaches for Early-Stage Hodgkin Lymphoma

<table>
<thead>
<tr>
<th>Trial</th>
<th>Timing of PET After ABVD</th>
<th>PET-Negative Deauville Score</th>
<th>Percent PET-Negative</th>
<th>Treatment Regimens</th>
<th>PFS, % (HR 95% CI)</th>
<th>Median Follow-up, Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>U.K. RAPID [27] (602 patients)</td>
<td>3 cycles</td>
<td>1–2</td>
<td>75</td>
<td>3 ABVD + 30 Gy IFRT (standard)</td>
<td>94.6 (ITT), 97.1 (PP)</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3 ABVD (PET−)</td>
<td>90.8 (ITT), 90.8 (PP) ITT: 1.57 (0.84–2.97)</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4 ABVD + 30 Gy IFRT (PET+)</td>
<td>87.6 PP: 2.36 (1.13–4.95)</td>
<td>5</td>
</tr>
<tr>
<td>EORTC H10 [28,29] (754 patients)</td>
<td>2 cycles</td>
<td>1–2</td>
<td>87</td>
<td>3 ABVD + 30 Gy INRT (standard)</td>
<td>99.0</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4 ABVD (PET−)</td>
<td>87.1 15.8 (3.8–66.1)</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2 ABVD + 2 EB + 30 Gy INRT (PET+)</td>
<td>90.6*</td>
<td>0.42 (0.23–0.74)</td>
</tr>
<tr>
<td>EORTC H10 [28,29] (1,196 patients)</td>
<td>2 cycles</td>
<td>1–2</td>
<td>78</td>
<td>4 ABVD + 30 Gy INRT (standard)</td>
<td>92.1</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6 ABVD (PET−)</td>
<td>89.6 1.45 (0.8–2.5)</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2 ABVD + 2 EB + 30 Gy INRT (PET+)</td>
<td>90.6*</td>
<td>0.42 (0.23–0.74)</td>
</tr>
<tr>
<td>CALGB-50604 [30] (164 patients)</td>
<td>2 cycles</td>
<td>1–3</td>
<td>91</td>
<td>4 ABVD (PET−)</td>
<td>92</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2 ABVD + 2 EB + 30 Gy IFRT (PET+)</td>
<td>66 6.0 (1.8–20.1)</td>
<td>2</td>
</tr>
</tbody>
</table>

*Includes both favorable and unfavorable risk patients with a positive interim PET scan. Abbreviations: ITT, intention to treat; PP, per protocol; EB, escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; CALGB, Cancer and Leukemia Group B.

for patients with bulky disease and those with a positive interim or end-of-therapy PET scan. To help individualize therapy, a thoughtful discussion is required in which other factors also must be considered to assess risk from primary therapy (i.e., the anatomic extent of disease and resultant normal tissue exposure to radiotherapy, cumulative toxicity of additional cycles of chemotherapy if radiotherapy is to be avoided, and added toxicity from salvage therapy). Therefore, chemotherapy alone may be preferred over CMT for a young woman younger than age 35 with mediastinal or axillary disease to avoid the risk of breast cancer. In contrast, for a young patient with bilateral neck disease, 2× ABVD plus 20 Gy ISRT would be a very effective approach.

CONCLUSIONS AND FUTURE DIRECTIONS

In summary, CMT remains the current standard of care for the majority of patients with ESHL. Ongoing studies continue to focus on reducing toxicity while maintaining or improving long-term cure rates. Radiotherapy doses and field size have evolved significantly over the past several decades and are expected to have a lower risk of cardiovascular disease and second cancers.30,33 Recent studies incorporating brentuximab vedotin (BV)34,35 and the PD-1 inhibitors nivolumab and pembrolizumab are summarized in Table 4. Pretreatment risk assessment with metabolic tumor volume, total lesion glycolysis, and serum thymus and activation-regulated chemokine levels may help define

TABLE 4. Trials Incorporating Novel Agents Into Frontline Therapy for Early-Stage Hodgkin Lymphoma

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patient Population</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT01868451</td>
<td>Unfavorable risk</td>
<td>BV-AVD + CVRT (30 Gy)</td>
</tr>
<tr>
<td>NCT03004833</td>
<td>Unfavorable risk</td>
<td>Nivolumab-AVD + IFRT (30 Gy)</td>
</tr>
<tr>
<td>NCT03226249</td>
<td>Favorable or unfavorable</td>
<td>Pembrolizumab-AVD</td>
</tr>
<tr>
<td>NCT03233347</td>
<td>Stage I to II nonbulky</td>
<td>BV-AVD + nivolumab consolidation</td>
</tr>
<tr>
<td>NCT02758717</td>
<td>Age &gt; 60</td>
<td>BV + nivolumab</td>
</tr>
<tr>
<td>NCT01716806</td>
<td>Age &gt; 60</td>
<td>BV + nivolumab, bendamustine, or dacarbazine</td>
</tr>
<tr>
<td>NCT02191930</td>
<td>Age &gt; 60, stage II bulky</td>
<td>BV + cyclophosphamide, doxorubicin, and prednisone</td>
</tr>
<tr>
<td>NCT02298283</td>
<td>PET-positive after 2 ABVD</td>
<td>BEACOPP + IFRT (30 Gy) + BV consolidation</td>
</tr>
</tbody>
</table>

Abbreviation: CVRT, conformational volume radiotherapy.
higher-risk patients at diagnosis in whom alternative approaches can be considered.\textsuperscript{36,37} Long-term follow-up is needed to determine the impact of these novel approaches.

**NEW RISK-ADAPTED TREATMENT STRATEGIES IN ADVANCED-STAGE HODGKIN LYMPHOMA**

The success that has been achieved in treating HL has provided a paradigm on which much of modern systemic oncologic treatment is based. It is imperative to achieve the greatest possible efficacy while minimizing toxicity, both during and after primary treatment. Randomized prospective clinical trials have proven pivotal to support evidence-based treatment planning complemented by the population-based evaluations needed to demonstrate effective translation into real-world settings.

**STAGING, PROGNOSTIC FACTORS, AND RISK ASSESSMENT**

Staging of HL is based on the Ann Arbor system, with the addition of a definition of bulky disease often referred to as the Cotswold modification.\textsuperscript{38} PET employing 18F-fluorodeoxyglucose has become essential not only to establish stage at diagnosis but also to provide a running assessment of treatment effectiveness both during and at the conclusion of primary treatment. Especially in the treatment of patients with advanced-stage disease, prognostic factor scoring systems can be helpful both in assessing and comparing clinical trial results and identifying patients at high risk of relapse. A robust prognostic model that identifies patients with differing risks of primary treatment failure was initially based on outcomes in approximately 5,000 patients with advanced-stage HL, most of whom had been treated with ABVD.\textsuperscript{39} Seven independent predictors of decreased likelihood of freedom from progression—sex, age, stage, hemoglobin level, white blood cell count, lymphocyte count, and serum albumin—can be combined in an International Prognostic Factors Score (IPS)\textsuperscript{40} to identify subgroups of patients with varying likelihood of freedom from progression based on the number of factors present at diagnosis (Table 5). Improvements in accuracy of diagnosis, staging based on PET, supportive care, and widespread use of high-dose chemotherapy and autologous hematopoietic stem cell transplantation (ASCT) for relapsed disease have lessened the discriminatory power of the IPS, as evidenced in the results we have seen at the BC Cancer Agency with 675 consecutive patients treated with ABVD or equivalent chemotherapy through 2009.\textsuperscript{41} The spread in 5-year freedom from progression has narrowed to 17% spread, ranging from 83% to 66%, and for the 94% of patients with advanced-stage HL who present with an IPS of 0 to 4, the 5-year OS has improved to approximately 90%. This change demonstrates that as overall treatment strategies improve, the impact of clinical prognostic scoring systems diminishes.

A large number of biologic characteristics of HL (biomarkers) with possible impact on risk have been identified, including a variety of biomarkers: antigens expressed on the HL Reed-Sternberg (HRS) cells; antigens expressed on circulating lymphocytes; antigens expressed on microenvironmental cells within the tumor; circulating biomarkers detectable in the serum; gene expression profiles of biopsied tumors; and specific germline polymorphisms.\textsuperscript{42} All are of interest; however, turning these interesting biologic observations into clinically relevant biomarkers for purposes of treatment planning has proven difficult, and, at present, they do not appear ready for integration into standard management.

A different set of risk factors relevant to HL are those that become evident during treatment. Treatment of advanced-stage HL is typically takes at least 6 to 8 months to complete. Poor quality of response during the delivery of multiple cycles of chemotherapy or absence of a complete response (CR) at the end of planned chemotherapy may identify patients with higher risk of relapse. The wide availability of PET imaging provides the opportunity to determine its usefulness in the management of both limited-stage HL and advanced-stage disease.

**POSITIVE INTERIM PET SCAN AS A RISK FACTOR FOR ADVANCED-STAGE HODGKIN LYMPHOMA**

ABVD is the only multiagent chemotherapy program for which interim PET has been evaluated extensively.\textsuperscript{26,43-49} Table 6 shows the outcome for patients treated with ABVD for advanced-stage HL, comparing results for those with a positive versus negative interim PET during ABVD chemotherapy. A negative interim PET is found in approximately 80% of patients, appears to be strongly predictive for a favorable outcome, and may largely override the prognostic impact of the IPS. However, for the approximately 20% of patients with a positive interim PET, the impact of a growing body of evidence suggests that the negative prognostic impact of a positive interim PET can be at least partially overcome by switching to intensified treatment such as escalated BEACOPP after a positive interim PET. This switch to intensified treatment may as much as double 2- to 3-year failure-free survival (Table 7). This substantial improvement in freedom from treatment failure is obtained at the cost of much higher toxicity using the alternative regimen, making the strategy of interim PET-guided intensification of treat-

### Table 5. Prognostic Factors Indicating Decreased Probability of Freedom From Progression in Advanced Hodgkin Lymphoma Treated With ABVD or an Equivalent Regimen

<table>
<thead>
<tr>
<th>Factor</th>
<th>Adverse Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender male</td>
<td>Age &gt; 45</td>
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<tr>
<td>Stage</td>
<td>IV</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>&lt; 105 g/L</td>
</tr>
<tr>
<td>White blood cell count</td>
<td>&gt; 15 × 10^9/L</td>
</tr>
<tr>
<td>Lymphocyte count</td>
<td>&lt; 0.6 × 10^9/L or &lt; 8% of the white cell differential</td>
</tr>
<tr>
<td>Serum albumin</td>
<td>&lt; 40 g/L</td>
</tr>
</tbody>
</table>
TABLE 6. Prognostic Impact of Interim PET Scan for Patients With Advanced-Stage Hodgkin Lymphoma Treated With ABVD

<table>
<thead>
<tr>
<th>Interim PET</th>
<th>N (%)</th>
<th>3-Year FFS, %</th>
<th>Treatment Failed, n (%)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>215 (83)</td>
<td>95</td>
<td>45 (17)</td>
<td>Biggi et al16</td>
</tr>
<tr>
<td>Positive</td>
<td>45 (17)</td>
<td>28</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>210 (81)</td>
<td>11 (5)</td>
<td>50 (19)</td>
<td>Gallamini et al49</td>
</tr>
<tr>
<td>Positive</td>
<td>50 (19)</td>
<td>43 (86)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>61 (79)</td>
<td>3 (5)</td>
<td>61 (79)</td>
<td>Hutchings et al26</td>
</tr>
<tr>
<td>Positive</td>
<td>16 (21)</td>
<td>11 (18)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

An alternative use of interim PET scan is to justify de-escalation of treatment intensity when PET negativity has been achieved. In such a strategy, treatment starts with intensified chemotherapy, such as escalated BEACOPP, and switches to lower intensification, perhaps ABVD, after an interim PET scan documents a high-quality response. The potential pros and cons of such a strategy are discussed below in the section on new approaches.

POSITIVE END-OF-CHEMOTHERAPY PET SCAN AS A RISK FACTOR FOR ADVANCED-STAGE HODGKIN LYMPHOMA

Persistence of viable tumor despite completion of planned chemotherapy for advanced HL is an obvious indicator of treatment failure and risk factor for recurrence. Although adding irradiation after the achievement of complete remission using multiagent chemotherapy for advanced-stage HL does not improve long-term outcome,10 the apparent ability of PET to identify patients with persistent active lymphoma has led to the advocacy of postchemotherapy irradiation when persistent disease is strongly suggested by a positive PET scan. Adding involved field radiation to a postchemotherapy residual PET-positive mass appears to improve a patient’s outcome to the same level as is achieved by patients who have a complete remission with either no residual mass or a PET-negative mass.51,52

NEW APPROACHES

Over the past 2 decades, two different approaches to overcoming treatment resistance in advanced-stage HL have emerged. The GHSG initially developed and refined a dose-escalated and accelerated chemotherapy program, escalated BEACOPP.53,54 Through a series of logical, well-designed clinical trials, this group demonstrated the superiority of escalated BEACOPP over regimens such as ABVD in terms of PFS, but documentation of superior OS has proven elusive,55 and many clinicians consider the increased short- and long-term toxicity of escalated BEACOPP too great to justify its use. More recently, however, a PET-adapted strategy in which a negative interim PET scan is used to prompt de-escalation to a reduced number of cycles of escalated BEACOPP has shown substantial promise.56 In the GHSG HD18 trial, 70% of patients with advanced-stage HL reached a PET-negative response after two cycles of escalated BEACOPP.56 Those then randomly assigned to complete treatment with two more cycles of escalated BEACOPP had a 5-year PFS of 92%, which was just as good as those randomized to complete treatment with four more cycles of escalated BEACOPP. Other investigators have evaluated de-escalation to regimens such as ABVD and in smaller, nonrandomized experiences have also shown excellent outcomes for patients with negative interim PET scans.48

An alternative approach to improving results for patients with advanced-stage HL has investigated the usefulness of adding a new therapeutic agent to the standard backbone of ABVD. The ECHLEON-1 trial randomized patients to standard ABVD versus doxorubicin, vinblastine, and dacarbazine (AVD) plus BV, an antibody drug conjugate directed against the CD30 antigen.57 The novel combination induced a superior freedom from treatment failure of 82% compared with 77% for those treated with standard ABVD. Of note, in the ECHLEON-1 trial, treatment was not guided by interim PET. All patients received their randomly assigned chemotherapy regimen. The novel regimen, AVD plus BV, appeared equally superior across multiple subgroups of patients, including those with high IPS scores, stage IV disease, and those with bone marrow or multiple extranodal sites of disease.

TABLE 7. Impact of Chemotherapy Escalation Based on Interim PET Scan for Patients With Advanced-Stage Hodgkin Lymphoma Treated Initially With ABVD: Phase II and Retrospective Trial Results

<table>
<thead>
<tr>
<th>Interim PET</th>
<th>N (%)</th>
<th>2-Year PFS, %</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>271 (82)</td>
<td>82</td>
<td>Press et al31</td>
</tr>
<tr>
<td>Positive</td>
<td>60 (18)*</td>
<td>64</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>41 (84)</td>
<td>82</td>
<td>Ganesan et al45</td>
</tr>
<tr>
<td>Positive</td>
<td>8 (16)</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>Approximately 80%</td>
<td>95</td>
<td>Gallamini et al47</td>
</tr>
<tr>
<td>Positive</td>
<td>Approximately 20%</td>
<td>62</td>
<td></td>
</tr>
</tbody>
</table>

*Eleven patients did not receive the randomly assigned escalation of chemotherapy due to patient refusal.

OVERALL TREATMENT STRATEGY AND FUTURE DIRECTIONS

The treatment of advanced-stage HL continues to evolve. Currently, the two best strategies that have emerged from clinical trials are either interim PET-guided escalation or de-escalation approaches or integration of the novel agent BV into primary chemotherapy. In the absence of a head-to-head comparison of these strategies, the final choice will appropriately remain with the treating specialist and should reflect careful discussion of the pros and cons of...
the different strategies. This final choice should be based on a full assessment of how to achieve the greatest efficacy while minimizing both short- and long-term toxicity. Future improvements in these already excellent results will likely involve further integration of novel agents, among which the checkpoint inhibitors appear to have the greatest potential.

BEYOND TRANSPLANT: NOVEL THERAPIES IN RELAPSED AND REFRACTORY HL

Prior to 2011, treatment options for patients with relapsed/refractory classic HL were limited to salvage chemotherapy and ASCT. With the approval of the antibody drug conjugate BV in 2011 and the immune checkpoint inhibitors nivolumab and pembrolizumab in 2016 and 2017, respectively, a new frontier has arrived. These new treatment modalities are changing the standard of care for patients with relapsed/refractory HL whose options were previously limited to cytotoxic chemotherapy. Still, many challenges remain as we study how to optimize the implementation of these therapies, including: how to determine which patients will benefit the most from which treatments, how to combine these agents with other novel agents or with standard chemotherapy, and whether these therapies can be incorporated into earlier lines of treatment. Given the curability of ASCT in up to 50% of relapsed/refractory HL, how should these therapies be sequenced with autologous and allogeneic SCT? As other novel therapies and novel combinations currently under investigation obtain approval, how will these be prioritized, sequenced, or combined with existing agents? Although this is an extremely exciting time for relapsed/refractory HL, the answers to these questions will hopefully advance still further the goals of increasing cure and minimizing toxicity for patients with relapsed/refractory HL.

BV

BV is an anti-CD30 monoclonal antibody attached to a cytotoxic antimitcrotubule agent monomethyl auristatin. BV was U.S. Food and Drug Administration approved for patients with relapsed/refractory HL who have failed either ASCT or at least two chemotherapy regimens, based on the pivotal phase II trial, which treated 102 patients with relapsed/refractory HL post-ASCT and demonstrated an overall response rate (ORR) of 75% with a CR rate of 34% and a median PFS of 5.6 months. In a follow-up study after a median observation period of 3 years, overall median PFS was 9.5 months, and OS was 40.5 months; an even greater PFS was seen in the 34 patients who achieved CR, with an estimated 3-year PFS of 58%; 16 of these patients (47%) remained progression-free after 53.3 months, with 6 receiving consolidative allogeneic SCT. These results suggest that a small subset of patients who achieve CR after treatment with BV may obtain long-term disease control. A longer follow-up period is needed to confirm these findings as well as improved methods to identify and characterize the mechanisms underlying these exceptional responses.

BV is also approved for consolidation post-ASCT based on the phase III AETHERA trial that compared 16 cycles of BV to placebo in 329 patients with relapsed/refractory HL who had undergone ASCT. An improvement in PFS was seen in the BV group (42.9 months) compared with placebo (24.1 months). Overall, therapy was well tolerated, with 47% of patients completing the full course of BV treatment; however, peripheral sensory neuropathy was the most common side effect in the BV group in 56% of patients receiving BV compared with 16% of placebo; 33% of patients receiving BV discontinued therapy due to adverse events compared with 6% of patients receiving placebo. No difference in OS between the two groups has been demonstrated in interim analysis. The applicability of these data to patients with relapsed/refractory HL with low-risk features who are in PET-negative CR prior to ASCT or in patients treated with BV prior to ASCT (as all patients in this study were BV naive) remains uncertain. It is also unclear how patients treated with up to 16 cycles of BV will respond to subsequent BV at time of relapse compared with patients who are not treated with maintenance therapy or who have been exposed to significantly less BV. Further analysis may delineate a subgroup of patients that will benefit most from consolidative therapy with BV post-ASCT.

CHECKPOINT INHIBITORS

HRS tumor cells comprise a small fraction (0.1%) of the cells in the HL microenvironment. Driven mainly by somatically acquired alterations of chromosome 9p24.1/CD274 (PD-L1)/PDCD1LG2 (PD-L2), HRS cells overexpress PD-L1 and PD-L2, which interact with PD-1 on peritumoral lymphocytes in the HL microenvironment and induce chronic activation and exhaustion. PD-L1 overexpression is not limited to HRS cells, but has also been reported in nonmalignant tumor-associated macrophages that are localized around PD-L1+ HRS cells. PD-L1+ tumor-associated macrophages are thought to promote tumor survival by protecting HRS cells from the cytotoxic effects of natural killer cells and tumor-specific cytotoxic T lymphocytes. Epstein-Barr virus latent membrane protein 1 has been shown to augment PD-L1 expression in Epstein-Barr virus–positive HL tumors mainly via AP-1 and JAK2/STAT signaling. Thus, there is a strong biologic rationale for targeting the PD-1 pathway in HL.

Nivolumab and pembrolizumab are immunoglobulin G4 monoclonal anti–PD-1 antibodies approved by the U.S. Food and Drug Administration for the treatment of relapsed/refractory HL in the initial CheckMate 039 trial, 23 patients with HL who progressed post-ASCT (78%) or BV (78%) were treated with nivolumab; a high ORR of 87% and PFS of 86% at 24 weeks was demonstrated. Nivolumab was approved based on the CheckMate 205 trial, in which 243 patients with relapsed/refractory HL who had failed ASCT were treated with nivolumab monotherapy, with an ORR of 69%, a CR of 16%, and overall median PFS of 15 months. These heavily pretreated patients were divided into three cohorts according to their BV status, with a slightly higher CR rate for the patients not previously treated with BV as compared with patients who received BV before or after ASCT (29% vs. 12% and 13%, respectively). Pembrolizumab was approved based on the KEYNOTE-87 trial that divided 210 patients with relapsed/refractory HL into three cohorts according to...
previous treatment with ASCT and/or BV, with all three cohorts showing an ORR of 69% and a CR of 22%.70

Both PD-1 inhibitors represent a noteworthy advance in the treatment of relapsed/refractory HL. However, the CR rate with monotherapy to both agents is modest, and relapses to these agents are seen even beyond 2 years. Ideally, rational combinations combining these with other agents may both deepen response and improve durability for more patients.

COMBINATION THERAPIES
Combination therapies are developed with the goal of choosing agents with a strong scientific rationale or complementary mechanisms of action and with toxicities that do not overlap. Bendamustine was combined with BV as pretransplant salvage therapy for relapsed/refractory HL in a phase I/II trial of 55 patients and demonstrated high activity, with an ORR of 93% and CR of 74%.71 Fifty-six percent of patients experienced infusion-related reactions, which caused premature termination of treatment in 24% of patients, although premedication with antihistamines and corticosteroids appeared effective in controlling these symptoms in those who were able to continue therapy.72 These results are comparable to the standard of care for first-line salvage of relapsed/refractory HL—high-dose chemotherapy with ifosfamide, carboplatin, etoposide—and may offer an alternative out-of-hospital salvage treatment option.72

In addition to the PD-1 pathway, the CTLA-4 pathway is a key target for checkpoint blockade therapy. Neoplastic HL cells are surrounded by a microenvironment of ineffective immune cells, fibroblasts, mesenchymal cells, and microvascularity that interact with the tumor cells, promoting cell growth and creating a favorable environment for immune evasion.66,73 Both PD-1 and CTLA-4 are negative regulators of T-cell immune function. In an effort to target these nonmalignant components and alter the permissive microenvironment from protective to cytotoxic, BV has been combined with the checkpoint inhibitors ipilimumab, a fully humanized immunoglobulin G1 monoclonal antibody targeting the CTLA-4 pathway, and the PD-1 inhibitor nivolumab. Preliminary results from 21 patients treated with BV and ipilimumab on the protocol E4412 (NCT01896999) demonstrated an ORR of 71% with a CR of 48% and a median PFS of 1.02 years with a median follow-up of 0.48 years; the median OS was not reached with a median follow-up of 1.16 years.74-75 The combination of BV plus nivolumab has been explored in both E4412 and in the trial NCT02572167 in the pretransplant first salvage setting.75,76 Interim results from both studies demonstrated a high ORR and CR rate: the E4412 trial showed an ORR of 89%, a CR of 50%, and a 6-month PFS of 91% for 18 patients, whereas the NCT02572167 trial had an ORR of 82% and a CR of 61%, with the majority of non-CR patients able to undergo further therapy and continue on to ASCT.75,76 Adverse events and immune-related toxicities occurred in both studies but were limited mainly to grades 1 and 2, with nausea, fatigue, and infusion-related reactions most common. Premedication was required for infusion reactions, but once treated, patients were able to continue on treatment in both studies. One grade 5 pneumonitis was reported in E4412.

Results from these studies have been promising, but clinical experience with these combinations remains limited at present. Further investigations are needed and ongoing to determine long-term tolerability and disease control before these combinations can be integrated into standard practice.

OTHER NOVEL THERAPIES
Beyond BV and checkpoint blockade, there are many other promising therapies currently under exploration in early-phase clinical trials. AFM13 is a bispecific anti-CD16A, anti-CD30 antibody that binds CD16A on natural killer cells and CD30 on HL tumor cells, resulting in natural killer cell activation and tumor cell lysis. In phase I as a single agent, the response to AFM13 monotherapy was 11.5%; however, there is a scientific rationale for combining AFM13 with checkpoint blockade, and a phase I study of this combination is currently underway in relapsed/refractory HL (NCT02656560).77 Chimeric antigen receptor (CAR) T cells are autologous T cells primed to target malignant cells and have shown encouraging antitumor activity in leukemia and non-HL.78,79 In data extrapolated from mice models, a CD123 antigen was identified for use as a target for CAR T cells and showed high therapeutic activity in a preclinical in vivo model of HL.80 In a separate study, 18 heavily pretreated patients with relapsed/refractory HL received CD30-specific CAR T cells; the ORR was 39% with no CRs.78 Although HRS cells are considered CD19 negative, an ongoing pilot study evaluated CD19 CAR T cells for the treatment of relapsed/refractory HL based on the rationale that HRS precursors and other supportive immune cells promoting cancerous cell survival may harbor the CD19 antigens. Four patients received CD19 CAR T cells and showed an ORR of 50% at day 28 with acceptable toxicities; however, only one patient achieved CR and progressed after 3 months.81 Lenalidomide is an immunomodulatory drug that was studied in 36 patients with relapsed/refractory HL who received a median of four prior therapies; the ORR was 19%, and 1 patient achieved CR.82 An ongoing trial is evaluating lenalidomide as maintenance therapy for patients with relapsed HL after ASCT (NCT01207921). The mTOR inhibitor everolimus demonstrated activity in a phase II study of heavily pretreated patients with relapsed/refractory HL with an ORR of 47%, with eight out of 19 patients achieving a partial response and a median PFS of 6.2 months.83 Histone deacetylase inhibitors have also been investigated; modest single-agent activity has been seen, and they are primarily under investigation as combination strategies with other novel agents. Panobinostat, a pan-deacetylase inhibitor, was evaluated in a phase I/II study in combination with the mTOR inhibitor everolimus, and the ORR for 13 patients with relapsed/refractory HL was 46%.84

CONCLUSION
Recent advances in HL biology have culminated in the development of many promising immunologic and targeted therapies for the treatment of relapsed/refractory HL. Despite these innovations, curative treatment of patients under the age of 75 with relapsed/refractory HL with good performance status remains high-dose chemotherapy followed by
ASCT.85,86 In the future, as we refine our prognostic tools and our ability to target therapy to biology, these agents or novel combinations will be integrated into earlier lines of therapy and may provide a bridge to successful SCT for greater numbers of patients, increase survival for patients relapsing post-SCT, or potentially replace SCT as a second-line salvage approach. Yet as these drugs move into earlier lines of therapy, many important questions remain unanswered with respect to both durability and long-term toxicity. What are the short- and long-term toxicities with immunotherapy, and will they be different in earlier lines of therapy for patients with more intact immune systems? If these agents are integrated into earlier lines of therapy, how will this change the options available for patients who subsequently relapse? Will checkpoint blockade combinations result in durable remission and at any point supplant SCT as second-line salvage? Ongoing and future investigations will hopefully answer these questions and, as more exciting therapies move from bench to bedside, offer a promise of increased cure with reduced toxicity for all patients with relapsed/refractory HL.

References


