

Risk- and response-adapted strategies for the management of Hodgkin lymphoma

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Abstract: Therapy for Hodgkin lymphoma (HL) is associated with excellent long-term survival rates, of 80% or more. Extended follow up has described late treatment-related toxicities, principally secondary malignancies, cardiovascular disease and infertility. Given the young age of many patients, there is a desire to offer a more personalised approach, correlated to individual tumour biology that enables treatment de-escalation in low risk patients to reduce toxicity, and treatment intensification in high risk patients to reduce treatment failure. Contemporary therapeutic strategies have involved risk assessment based on staging and clinical factors. The use of functional imaging with 18F-fluorodeoxyglucose positron emission tomography (18F-FDG-PET) as a predictive tool to identify early non-responders has been well validated and outperforms the risk stratifying International Prognostic Score (IPS). HL has particularly high FDG-avidity (97-100%), with FDG-PET scanning reflecting metabolic activity and acting as a surrogate biomarker for chemosensitivity. International consensus on the methods of reporting and interpreting FDG-PET scans has enabled their use to be standardised and reproducible. Given that primary therapy fails for 15-20% of patients, the use of combined FDG-PET and computerised tomography (FDG-PET/CT) to provide a response-adapted strategy to guide management is under investigation in numerous prospective clinical trials. They aim to determine whether early response scanning can be used to directly modulate subsequent therapy, through intensifying or abbreviating chemotherapy regimens and/or omitting radiotherapy. Integrated multi-modality imaging and advanced conformal planning techniques have led to the emergence of radiotherapy strategies such as involved-node radiation (INRT) that aim to optimise treatment volumes and maintain efficacy whilst lowering toxicity. Study groups have incorporated these modalities in trial designs to assess whether a PET-directed, individualised approach can become the new standard of care.

Keywords: Combination of doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD); BEACOPP; 18F-fluorodeoxyglucose positron emission tomography (18F-FDG-PET); Hodgkin lymphoma (HL); involved-node radiation (INRT); risk-adapted

Submitted Mar 18, 2015. Accepted for publication Mar 19, 2015.

doi: 10.3978/j.issn.2304-3865.2015.03.04

View this article at: <http://dx.doi.org/10.3978/j.issn.2304-3865.2015.03.04>

Introduction

Biological insights, new therapies and incremental clinical trial evidence have allowed treatment strategies that result in cure rates for Hodgkin lymphoma (HL) of 80% and higher. Unusually among malignancies, cures in HL can be achieved with both primary therapy, and in many cases with salvage therapy for refractory or relapsed disease, making the assessment of therapeutic benefit more complex, and dependent upon long follow up. A consequence of the high survivorship in a patient population with a peak among young adults is the risk of late adverse effects from therapy. Radiotherapy and chemotherapy can variously induce second malignancies, cardiovascular disease and infertility, with an incidence strongly correlated to the intensity of the initial therapy. In considering the optimal treatment of HL, a balance has to be struck between the need to maintain treatment intensity to maximise cure rates, whilst taking measures to limit excessive early or late toxicity. In doing this, selecting patients with unfavourable disease at presentation or who do not show an early treatment response, for selective intensification of therapy, may provide a means to achieve the correct approach. The widespread use of functional imaging with 18F-fluorodeoxyglucose positron emission tomography (18F-FDG-PET) has enabled investigators to identify non-responders early during treatment. The primary treatment of both early and advanced stage HL has been progressively refined through clinical trials that address the optimal approach with combined or single modality therapy.

Primary therapy

Primary treatment is guided by the clinical stage of disease as described by the Cotswold classification (1) and updated by the Lugano classification to incorporate the use of FDG-PET/computerised tomography (CT) imaging in baseline assessment (2). Patients are divided into early (stage I and favourable stage II) or advanced (high risk stage II, stages III and IV) disease. The standard approach to treatment is with combined chemotherapy and radiotherapy in early disease and predominantly chemotherapy, sometimes followed by consolidation radiotherapy, in advanced stages. The combination of doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) has become a standard approach in many centers, over three decades after the original randomised control trial demonstrated complete remissions in 75% with a tolerable side effect profile (3) (see *Table 1*).

Contemporary prospective trials have confirmed favourable outcomes with ABVD, reporting complete response rates of 73-89%, 5-year freedom from progression (FFP) of 73-76% and 5-year overall survival (OS) of up to 90% in intermediate and advanced stage HL (4-7). Many attempts to improve upon these results using more complex regimens have proven negative, but one which leads to consistently better tumour control is the escalated BEACOPP regimen (*Table 2*), developed by the German Hodgkin Study Group (GHSG). It is mostly used as primary therapy in advanced HL after demonstrating greater efficacy over the alternating COPP-ABVD regimen (8,9). After 10 years of follow-up eBEACOPP was associated with a freedom from treatment failure (FFTF) rate of 82%, OS of 86% and second malignancy rate of 6% in patients with advanced stage HL (10). Direct comparative studies have sought to address the question of which regimen is superior, with the conclusion that eBEACOPP produces higher response rates and greater tumour control with prolonged progression-free survival (PFS) but minimal improvement in OS, owing to the efficacy of second line therapy (11-14). A recent systematic review suggested that six cycles of eBEACOPP might give a survival advantage of 7% over ABVD in advanced stage HL (5-year OS; 95% *vs.* 88%, respectively) (15). This however is at the expense of more acute toxicity, infertility in many cases and a slightly higher risk of secondary acute myeloid leukaemia or myelodysplastic syndromes, although the total number of secondary malignancies has not been shown statistically different to ABVD (12). The main arguments in favour of selecting ABVD over eBEACOPP are lower acute grade 3/4 toxicities, principally myelosuppression (leukopenia 22% *vs.* 98%; thrombocytopenia 3% *vs.* 70%; anaemia 5% *vs.* 66%), infection (2% *vs.* 22%), nausea (13% *vs.* 20%), and alopecia (31% *vs.* 79%) (16,17). ABVD is associated with fewer hospital admissions with neutropenic sepsis and significantly lower rates of infertility (18,19).

Prognostic factors at diagnosis

Early stage disease has been stratified into favourable and unfavourable prognostic groups based on age, the presence of B symptoms, number of nodal sites involved, and the maximum size of adenopathy (20,21) (see *Table 3*). The International Prognostic Score (IPS) for HL was devised as a risk stratification tool for advanced HL that defined adverse prognostic factors at diagnosis based on seven clinical parameters (low albumin, anaemia, male gender, increasing age, advanced stage, leukocytosis, and lymphopenia) (22).

Table 1 The ABVD regimen

Drugs	Dosage (mg/m ²)	Route of administration	Time
Adriamycin (doxorubicin)	25	i.v.	Days 1-15
Bleomycin	10,000 units/m ²	i.v.	Days 1-15
Vinblastine	6	i.v.	Days 1-15
Dacarbazine	375	i.v.	Days 1-15

Repeat cycle every 28 days. Early disease: 2-4 cycles +/- radiotherapy; advanced disease: 6-8 cycles.

Table 2 Comparison between different BEACOPP regimens

Drugs	The escalated BEACOPP regimen			BEACOPP-14 or standard BEACOPP		
	Dosage (mg/m ²)	Route of administration	Time	Dosage (mg/m ²)	Route of administration	Time
Bleomycin	10,000 units/m ²	i.v.	Day 8	10,000 units/m ²	i.v.	Day 8
Etoposide	200	i.v.	Days 1-3	100	i.v.	Days 1-3
Adriamycin	35	i.v.	Day 1	25	i.v.	Day 1
Cyclophosphamide	1,250	i.v.	Day 1	650	i.v.	Day 1
Vincristine	1.4 (max. 2 mg)	i.v.	Day 8	1.4 (max. 2 mg)	i.v.	Day 8
Procarbazine	100	p.o.	Day 1-7	100	p.o.	Days 1-7
Prednisone	40	p.o.	Day 1-14	40-80	p.o.	Days 1-7 (80 mg/m ²); days 1-14 (40 mg/m ²)
G-CSF	5 mg/kg	s.c.	From day 8	5 mg/kg	s.c.	From day 8

The escalated BEACOPP regimen repeats cycle every 21 days for up to 8 cycles; BEACOPP-14 repeats cycle every 14 days; standard BEACOPP repeats cycle every 21 days.

Table 3 Early stage HL (stage I-II): definitions of unfavourable risk disease

- Large mediastinal mass, size at least one third of the maximum thorax diameter[†]
- Extra-nodal disease^{*†}
- Involvement of three or more nodal areas[†]
- Elevated erythrocyte sedimentation rate (>50 mm/h for stages IA, IIA and >30 mm/h for stages IB, IIB)[†]
- Age >50 years[§]

[†], defined by GHSG (20); *, extra-nodal involvement is defined as localized involvement of an extra-lymphatic tissue (by continuous growth from an involved lymph node or in close anatomic relation) that is treatable by irradiation; [§], defined by EORTC (21). HL, Hodgkin lymphoma; GHSG, German Hodgkin Study Group.

This data collection from over 5,000 patients reflected outcomes for those treated mainly in the 1980s, while recently the IPS was re-tested in 740 patients with advanced-stage HL treated in British Columbia over a 30-year period (23). The study found that overall 5-year FFP had improved from 42% to 62%, the IPS retained its prognostic statistical significance, but as the results improved it was not possible to identify a patient group with sufficiently poor prognosis to justify intensified first-line therapy.

The one group with persistently worse outcomes is the elderly, owing to lower response rates, co-morbidity, lower success rates with salvage therapy and excess deaths from other causes including infections, second malignancies and cardiac disease (24,25).

The limitations of clinical prognostic models have led to the evaluation of molecular and immune-based biomarkers. These include assessment of circulating microRNA (26), infiltrating immune cells such as macrophages (27), the

presence of Epstein-Barr virus (28-30), circulating cytokines (31-33), chemokines (34) and surface proteins such as CD30 (35,36), produced by malignant and host immune cells. Gene-expression profiling has identified a transcript signature of tumour associated CD68+ macrophages, whose frequency is directly correlated with treatment failure and survival, outperforming the IPS as a single prognostic biomarker (37). More limited but logistically practical technologies to measure RNA-based gene expression on formalin-fixed paraffin-embedded tissue will soon enable testing to enter the routine diagnostic workup (38). A 23-gene panel has been developed which may identify patients at diagnosis who are at increased risk of treatment failure and death owing to the underlying tumour biology and suppressed anti-tumour immunity (39). These biomarkers may hold promise for the definition of prognosis based upon biology rather than more general clinical findings, but they still require prospective validation before they enter routine use.

Functional imaging with FDG-PET

HL has a FDG avidity rate of 97-100% and when used alongside CT imaging this can lead to a change in stage in 10-30% of patients at baseline (2). Bone marrow biopsy is no longer part of routine staging owing to the high sensitivity (88-100%) and specificity (87-100%) of FDG-PET/CT to detect bone marrow involvement (40-42). The use of FDG-PET imaging to detect residual metabolically active disease is well validated in this context, effectively acting as a surrogate biomarker for chemosensitivity. Superseding the prognostic value of the IPS, and superior to CT, a positive FDG-PET scan after two cycles of ABVD is independently highly predictive of relapse and poorer OS (43-47). Advanced HL has a negative predictive value (NPV) of 97-100% and a positive predictive value (PPV) of 13-27% (48), with one study reporting a NPV of 73% (49). Patients with a PET-2 negative scan have a 2-year PFS of 96% compared to 0-6% for PET-2 positive patients (45). Multivariate analysis demonstrated that the IPS loses its prognostic value when compared with PET-2 since PET-2 positive patients have an equally high risk of treatment failure with both high and low IPS, and conversely, PET-2 negative patients have an equally low risk of treatment failure with both high and low IPS. FDG-PET imaging is interpreted using the Deauville 5-point scoring system (5PS) (50,51). This is well validated and reproducible, however, central review is still preferable in the context of clinical trials. A PET 5PS of 1-2 is considered 'negative',

4-5 is considered 'positive', whilst a score of 3 is variably interpreted according to the objectives of the trial (52).

The correct timing of FDG-PET scanning is important as test sensitivity can be compromised by the immediate effect of chemotherapy stunning on cellular glucose metabolism (53). In addition, FDG-PET scans should not be performed 7-10 days post chemotherapy during the peak of the inflammatory response to avoid misinterpretation (54,55). The optimal timing of PET-2 scanning is 11-13 days after the second cycle of chemotherapy, prior to the day 14 treatment, within a 28-day cycle (56). Following completion of primary therapy FDG-PET imaging should be performed 3-6 weeks from the final chemotherapy or 12 weeks from completing radiotherapy to avoid a radiotherapy-induced inflammatory response (53,54).

Treatment of early stage favourable Hodgkin lymphoma (HL)

For patients with early stage favourable disease, large randomised trials have helped to define the optimal treatment choices: chemotherapy alone, or combined modality therapy. Radiation therapy alone can elicit cures, however combined modality strategies reduce relapse rates, the need for subsequent salvage therapy and thereby the overall rate of second malignancies (57). Extensive radiation therapy is associated with the development of secondary malignancies 5 to 25 years after primary treatment (58-60), leading investigators to seek reduced exposure, or to eliminate radiation altogether. An historic meta-analysis of 23 randomised trials involving 3,888 patients with early stage HL showed combined chemotherapy and involved field radiotherapy (IFRT) improved disease-free survival compared to radiotherapy alone, halving the 10-year risk of treatment failure (16% *vs.* 33%; $P < 0.00001$), although the efficacy of salvage chemotherapy after radiotherapy alone meant that there was no clear difference in OS at 10 years (61).

The EORTC H8-F trial demonstrated a 5-year event-free survival (EFS) rate significantly higher after three cycles of MOPP-ABV plus IFRT than after subtotal nodal radiotherapy alone (98% *vs.* 74%, $P < 0.001$). The 10-year OS estimates were 97% and 92%, respectively ($P = 0.001$) (62). Standard approaches now include ABVD for a variable number of cycles, with or without radiation therapy. A few trials have tested the merit of a chemotherapy-alone strategy. In one, there was no significant difference in relapse rate or OS between those having or omitting extended irradiation after 6 ABVD (63), while in the North American Children's

Oncology Group study, patients with complete remission after chemotherapy were randomized to low-dose (21 Gy) IFRT or no further therapy (64). The trial was stopped when an interim analysis revealed a significant difference in PFS between the arms, and with a median 7.7 years follow-up, there was a significant difference in EFS favouring the radiotherapy group (93% *vs.* 83%, $P < 0.004$). However, there was no difference in OS, with 10-year estimated survival rates of 96-97%, across all risk groups. A larger trial among adults of chemotherapy alone group resulted in improved OS at 12-year compared to chemotherapy plus extended-field radiotherapy (EFRT) (94% *vs.* 87%, respectively) (65). However, this was confounded by an increased rate of death from other causes in the combined modality group, and the use of EFRT, which is no longer used, being known to cause greater late toxicity compared with modern radiotherapy techniques. Other randomised trials, meta-analyses and population-based studies in early stage disease have shown superior tumour control with a combined treatment approach compared to chemotherapy alone (66-69).

Contemporary trials have focused on optimising a combined modality strategy. The GHSG HD10 'non-inferiority' trial randomly assigned 1,370 patients with favourable prognosis early stage HL to receive two or four cycles of ABVD with 20 or 30 Gy of IFRT (20). At a median follow-up of 7.5 years, there was no significant difference between four and two cycles of ABVD chemotherapy (5-year OS, 97% *vs.* 97%; FFTE, 93% *vs.* 91%) or between 30 Gy and 20 Gy IFRT (5-year OS, 98% *vs.* 97.5%; FFTE, 93% *vs.* 93%). However, there were significant differences in major toxicity between four and two cycles of ABVD (grade ≥ 3 overall toxicity; 52% *vs.* 33%) and between 30 and 20 Gy IFRT (grade ≥ 3 overall toxicity; 9% *vs.* 3%). This trial demonstrated that the duration and intensity of first line treatment could be reduced while maintaining tumour control by using two cycles of ABVD followed by 20 Gy IFRT over a three-month period. In a follow-on study, GHSG HD13, 1,502 patients with favourable prognosis early stage HL received two cycles of ABVD, omitting dacarbazine and/or bleomycin, followed by 30 Gy IFRT (70). FFTE at 5-year was significantly lower in the chemotherapy omitted groups, suggesting that both these drugs make a significant contribution to cure rates.

Treatment of early stage unfavourable Hodgkin lymphoma (HL)

The standard treatment for early stage, unfavourable

prognosis HL is combination chemotherapy with ABVD (four to six cycles) followed by IFRT or involved-node radiation (INRT). As with favourable prognosis early HL, a subset of patients with non-bulky disease or those with increased susceptibility to long-term radiotherapy complications may be adequately treated with chemotherapy alone when this is given for additional cycles.

The two key GHSG trials in intermediate stage/early unfavourable prognosis HL are the HD11 and HD14 trials. The HD11 trial compared four cycles of ABVD versus four cycles of BEACOPP, with each arm receiving either 20 or 30 Gy IFRT (71). BEACOPP was associated with increased severe toxicity and showed no additional benefit in disease control over ABVD when given with 30 Gy IFRT. However, 20 Gy IFRT was inferior to 30 Gy when given after four cycles of ABVD. The HD14 trial demonstrated improved tumour control, but not improved survival, with two cycles of eBEACOPP plus two cycles of ABVD with 30 Gy IFRT (2+2 arm) compared to four cycles of ABVD plus 30 Gy IFRT (5-year FFTE 95% *vs.* 88%, respectively; OS 97% each; $P < 0.001$) (72). Despite the significantly increased acute toxicity with eBEACOPP (grade ≥ 3 overall toxicity; 87% *vs.* 51%), the authors suggested a 2+2 strategy was preferable in a broader context as fewer patients progressed (2.5% *vs.* 8.4%; $P < 0.001$), thereby averting salvage chemotherapy and its toxicity.

Risk adapted radiotherapy—involved-node radiation (INRT)

Trials involving combined modality approaches in early stage HL have largely used IFRT with doses 20 to 40 Gy, given in single fractions of 1.8 to 2.0 Gy (62,73-75). In addition to lowering the radiation dose there has been a focus on reducing the field size to limit toxicity without compromising tumour control. EFRT, which includes adjacent uninvolved sites (e.g., mantle field), has been superseded by IFRT limited to involved regions only (e.g., mediastinal irradiation). A retrospective study of female Hodgkin's survivors exposed to either EFRT or IFRT reported an overall cumulative incidence at 30 years of breast cancer of 26% in those treated before the age of 21 (76). An increased field size with EFRT compared with similarly dosed IFRT (36-44 Gy) was associated with a 2.7-fold increased breast cancer risk. Cardiovascular complications directly related to field size include accelerated atherosclerosis causing coronary artery disease, cardiac valvular fibrosis and radiation pericarditis (77).

Cardiovascular disease represents the most common non-malignant cause of death in long-term survivors (60,78,79). When the heart is within the irradiated field, there is a dose-dependent relationship with doses above 15 Gy, with the incidence of biventricular failure, myocardial infarction, pericardial and valvular disease occurring two- to six-fold higher than in non-irradiated survivors (80). Patients with pre-existing heart disease are at 20% increased risk of cardiac hospitalisation by 10 years when treated with primary mediastinal radiotherapy alongside anthracycline-containing chemotherapy, compared to chemotherapy alone (81). As a consequence the risk of requiring cardiac procedures was up to nine-fold higher than the general population (82). These interventions included coronary artery bypass grafting, angioplasty and valve surgery.

The increasing sophistication of modern radiotherapy conformal planning and cross-sectional imaging has facilitated a move to further reduce field sizes with involved-site radiation (ISRT) and INRT delivering treatment to only detectable nodes (and extranodal lesions) identified at presentation (83). New treatment techniques include image-guided radiotherapy, four-dimensional imaging, deep-inspiration breath-hold (DIBH) and intensity modulated radiotherapy (IMRT) (84). ISRT is more conservative than INRT with the radiation field including only pre- and post-chemotherapy tumour volumes compared to pre- and post-chemotherapy nodal volume (85). Both techniques include a margin of healthy tissue of under 1 cm and use the pre-chemotherapy gross tumour volume (GTV) to determine the clinical target volume (CTV). The key distinction between the two techniques is that INRT integrates imaging with contrast-enhanced CT, fused FDG-PET/CT and MRI with 3-dimensional (3D) planning to further reduce the CTV. In INRT the pre-chemotherapy FDG-PET/CT is fused with the post-chemotherapy planning CT scan enabling the CTV to be contoured whilst sparing uninvolved surrounding structures such as heart and lungs. The patient must undergo baseline imaging in the planned RT position. Comparison of baseline and post-chemotherapy imaging identifies initially involved lymph nodes that had subsequently shrunk or vanished (86). INRT post ABVD has been validated by several studies, showing it to be safe and achieving excellent tumour control in early stage HL with 4-year FFTR of 96% and 5-year PFS of 92% with radiation doses of 30-40 Gy (84,87). The GHSG showed a significant reduction in the planning target volumes (PTV) of 20 patients with early mediastinal HL, with a median PTV of 1,705 cm³ with IFRT and 1,015 cm³

with INRT (88). INRT results in reduced radiation to organs at risk (OAR) with a mean dose to the heart of 17.94 Gy (3D-IFRT) *vs.* 9.19 Gy (3D-INRT) and 13.76 Gy (IF-IMRT) *vs.* 7.42 Gy (IN-IMRT). IMRT reduces OAR volume exposed to high doses and is superior for large PTVs involving the anterior mediastinum. Studies with involved-node proton therapy have further reduced the median dose to OAR compared to IN-IMRT and 3D-INRT owing to the unique radiobiology of proton therapy (89). Modern radiotherapy is likely to be shaped by an individualised, highly conformal approach guided by integrated multi-modality imaging.

Response-adapted therapy for early Hodgkin lymphoma (HL)

Controversy over the omission of radiotherapy in early HL has led to the testing of FDG-PET imaging as a means to select those patients who may not require irradiation after chemotherapy. A recent retrospective study assessed the predictive value of FDG-PET scanning after two cycles of ABVD (PET-2) on 2-year failure-free survival (FFS) following treatment with four cycles of ABVD plus IFRT in early HL (90). A total of 15% of patients had a PET-2 positive scan, and after central review the predictive value of PET-2 on PFS was characterised by a very high NPV (95%) and specificity (92%), a low PPV (53%) and sensitivity (65.5%), and an accuracy of 89%. The study found the presence of bulky disease within early stage HL could negatively influence the specificity and PPV of PET-2.

The EORTC H10 study in early HL tested the capacity of FDG-PET scanning after two cycles of ABVD to guide subsequent treatment (91), randomising patients between either standard or PET-directed algorithms. The standard arm for favourable HL was 3 ABVD with 30 Gy INRT, while in the experimental arm a negative PET after two ABVD was followed by two further cycles but no irradiation, and those with a positive PET scan received two cycles of eBEACOPP followed by 30 Gy INRT. For unfavourable disease the standard was 4 ABVD with 30 Gy INRT, while the PET-guided arm used six ABVD for those PET-negative after two cycles, or eBEACOPP with 30 Gy INRT for those remaining PET-positive. A pre-planned interim futility analysis revealed a small but significant increase in early treatment failure in the chemotherapy alone group where radiotherapy was omitted following an early negative PET scan, although the results may have been affected by lack of central review of the scans and the

absence of local blinding of the reporting. Nonetheless both trial arms had excellent outcomes with 1-year PFS of 95% and 97%, respectively.

The UK RAPID trial used FDG-PET response-directed therapy following three cycles of ABVD in early HL to randomised PET-negative patients between IFRT and no further radiotherapy (NFT) (92). Analysis after a median 5 years follow up showed the PFS at 3 years to be 94.6% in the irradiated group and 90.8% in the non-irradiated, with no difference in overall survival: 97.1% in the irradiated and 99% in the non-irradiated group. The investigators concluded that excellent outcomes are achievable without radiotherapy in selected cases, albeit with a slight increase in the risk of recurrence.

The GHSG HD16 trial is currently recruiting 1,100 favourable early stage HL patients and randomising those who are PET negative after two cycles of ABVD to receive either 20 Gy IFRT or no further treatment (NCT00736320).

Treatment of advanced stage Hodgkin lymphoma (HL)

Opinion is divided as to whether 68 cycles of ABVD or six cycles of eBEACOPP should be the standard of care for advanced HL. The use of interim FDG-PET scanning to identify early non-responders provides a response-adapted approach whereby those with PET-positive disease after two cycles of ABVD can be risk stratified and go on to receive the more intensive eBEACOPP. Conversely, investigators have examined the role of early FDG-PET scanning as a means to de-escalate treatment to avoid unnecessary toxicity in early responders. In contrast to early stage HL, maximising treatment efficacy takes precedence over limiting toxicity.

Several randomised trials are currently evaluating PET-directed therapy in advanced HL. Studies designed to assess whether early PET negative scans can de-escalate standard therapy include the RATHL study comparing ABVD with AVD (bleomycin omitted) (93,94), the GHSG HD18 trial, investigating 6 versus 4 cycles of BEACOPP, the Italian lymphoma study group HD0801 trial, investigating 30 Gy RT versus no RT after six cycles of ABVD, and the Group pour l'Etude des Lymphomes de l'Adulte (GELA) AHL and Israeli RHC trials both comparing BEACOPP versus ABVD. The studies all have the primary endpoint of PFS of between 2 to 5 years. The GHSG HD18 trial uses a four-point scale for interim FDG-PET interpretation, similar to

the Deauville 5PS; however since the principal objective was to test de-escalation, researchers chose a more conservative cut-off for a positive PET scan in an attempt to reduce false-negative results (95). This has resulted in a higher PET-2 positive rate of 47% after two cycles of eBEACOPP (56), and stands in contrast to a rate of 15-20% with ABVD in three of the other PET-directed trials (94,96,97).

Studies evaluating whether early PET positive scans can be used to escalate standard therapy include the RATHL study (93), escalating ABVD to either six cycles of BEACOPP-14 or four cycles of eBEACOPP, the US Intergroup S0816 trial (97), escalating ABVD to six cycles of eBEACOPP, the Italian lymphoma study group HD0607 trial (96), escalating ABVD to four cycles of eBEACOPP and four baseline BEACOPP, the GHSG HD18 trial (95), investigating the addition of Rituximab to eBEACOPP, and the Israeli RHC trials both comparing escalating eBEACOPP or ABVD to eBEACOPP with or without INRT.

Some trials start with eBEACOPP and de-escalate to ABVD with a negative PET-2, whilst other trials start with ABVD and escalate to eBEACOPP with a positive PET-2. These are clearly alternative strategies, with the critical difference being that escalated therapy will affect a much smaller patient subset, of approximately 15-20% with a positive interim PET scan. Preliminary results from the Italian HD0607 trial have shown a 15% positive PET-2 rate following two cycles of ABVD, with 41/222 patients escalated to four cycles of eBEACOPP plus four cycles of stdBEACOPP, with 73% achieving complete remission (96). The 1-year PFS in the PET-2 positive group was 80.5%, demonstrating the merits of an early switch in therapy. The majority (64%) of positive PET-2 scans had residual FDG uptake from a single bulky mediastinal site (98). A retrospective trial that analysed an identical strategy of escalated therapy reported a 2-year FFS of 91% overall, and 62% in the escalated PET-2 positive group (99), which was clearly superior to historical prospective trials that reported a 2-year FFS of 80% overall (100,101), and just 12% in the PET-2 positive group maintained on ABVD (45).

Results from the UK RATHL trial have demonstrated a PET-2 negative rate of 84%, with a PFS event rate of 9% in the first year among this group (93). Patients had less deterioration in lung function if they were randomised to stop bleomycin (mean change in diffusion capacity; 4.3% *vs.* 12.8%) (94). Longer term treatment failure rates and survival data are awaited, to determine whether this was linked to any difference in efficacy. In the PET-2 positive

arm, patients escalated with eBEACOPP or BEACOPP-14 achieved CR in 76%, at completion FDG-PET scanning (PET-3). The response rates did not differ between the two intensified BEACOPP regimens. The rate of treatment failure was 22% in the PET-2 positive arm. These initial results suggest that early FDG-PET scanning may be a useful tool for treatment modulation, both for escalating and de-escalating therapy.

Failure of primary therapy

Patients with primary refractory or relapsed disease may still be cured with salvage regimens and high dose consolidation therapy, with those who received more intensive chemotherapy (alternating MOPP/ABVD or BEACOPP) being harder to salvage successfully than those who received ABVD (102,103). Predictably, performance status, age above 50 years and the ability to tolerate salvage chemotherapy and ASCT directly impacts on survival (104,105). Primary refractory disease carries a poorer prognosis than relapsed disease after primary therapy (106). In relapsed disease, short time to relapse (within one year of completing induction therapy), advanced stage at relapse, and anaemia are poor prognostic factors (107). The use of FDG-PET scanning prior to ASCT is strongly predictive of subsequent relapse, with one study demonstrating an EFS of >80% if PET-negative pre-ASCT, compared to 29% if PET-positive (108).

Conclusions

Recent studies have explored a risk-adapted strategy to HL, using early FDG-PET scanning to guide therapy by acting as a marker of chemosensitivity. PET-2 scanning is highly predictive of outcome in patients with advanced HL treated with ABVD (45), especially when reading is standardised using the 5PS, rather than the use of standardised uptake values (SUV). The scale provides reproducible results with a high level of concordance seen across studies (51,109). The cut-off for a positive and negative PET scan can be adapted according to the clinical trial design, in order to avoid over-treatment or under-treatment. A PET tailored approach appears promising, but until the current studies report their primary endpoints, changing treatment based solely on interim PET scanning cannot be mandated as a standard of care (52). As a result, the optimal management of ABVD-treated patients with advanced stage HL who have a positive PET-2 remains uncertain: current recommendations are

that treatment should not be altered unless there is clear evidence of disease progression or unacceptable toxicity (48). In early stage HL, if a pre-treatment plan has been made to give primary therapy with ABVD followed by radiotherapy, then there is no clear role for early PET assessment (52). However, end of treatment FDG-PET/CT is recommended for all patients to inform on the need for radiotherapy, further biopsies and follow-up schedules.

The current standard of care for early stage HL is two cycles of ABVD and 20 Gy radiotherapy for favourable prognosis, and four cycles of ABVD and 30 Gy for unfavourable prognosis (52). If radiotherapy is to be omitted on the basis of a negative post-chemotherapy PET scan then patients should receive a minimum of three cycles of ABVD and should be aware of the slight increase in the risk of recurrence. However, radiotherapy is recommended for early stage patients with bulky disease. Combining two cycles of eBEACOPP with two cycles of ABVD and 30 Gy is a treatment option in early unfavourable HL, as per the HD14 trial protocol (72).

The standard of care for advanced HL in patients aged 16 to 60 is either 6-8 cycles of ABVD or six cycles of eBEACOPP, with consideration given to the differences in efficacy and toxicity between these two regimens. Consolidation radiotherapy is recommended for ABVD-treated patients to sites of original bulky disease or where there is residual tissue is >1.5 cm on CT, although the early results of the PET-negative arms in RATHL are promising and may in due course provide evidence that radiotherapy can be avoided for this group. PET-negative patients who received eBEACOPP do not require consolidation radiotherapy to residual tissue (52).

The treatment of HL continues to evolve, and the studies now in progress or in follow up promise to further refine the approach, maintaining the high expectation of cure but also lowering the risk of long-term morbidity.

Acknowledgements

Disclosure: PW Johnson has received honoraria for participation in advisory boards and educational symposia from Millenium-Takeda and Bristol Myers Squibb.

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Cite this article as: Remer M, Johnson PW. Risk- and response-adapted strategies for the management of Hodgkin lymphoma. *Chin Clin Oncol* 2015;4(1):13. doi: 10.3978/j.issn.2304-3865.2015.03.04