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How I treat advanced Hodgkin lymphoma — a global view

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Introduction (P. Hokland)

We haematologists always seek to follow standardized guidelines of practice and apply the best treatment for our patients with blood diseases within our means. However, treatment can never follow an exact recipe. Opinions differ as to the best approach, sometimes more than one treatment approach results in identical outcomes, or treatments differ only by the manner in which they fail. Furthermore, the haematologist is faced with constraints relating to the local economic environment. Patients too are not the same the world over. Early presentation is commoner in the developed world, as is the patient's understanding of the disease process. This in turn impacts the way patients are managed, the rigorousness of patient adhesion to the treatment schedule and the outcome.

For these reasons, given the same starting conditions, patients will be treated differently according to the institute and the country they are in. In this series of global views, we have tasked experts from around the world to describe their management plan and rationale for a specific disease presentation. Here we explore the management of Hodgkin lymphoma (HL) at six different institutes worldwide. We finish with a conclusion from a lymphoma expert comparing and contrasting these different management styles, weighing in on their merits

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Peter Hokland devised the concept and wrote the case story. The authors from the different countries wrote their own contributions separately. Judith Trotman reviewed these and wrote the concluding remarks.

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and limitations. The case history and questions posed to the experts are shown in Box 1 and their responses are summarized in Table I.

We hope that this exercise brings home to practising clinicians that there is more than one "right" way to manage patients. There are always things to learn from the way other experts practice. Moreover, there is much to learn from our colleagues working in strained economies. That teaches us that we should be nuanced in our perception of how and why treatments differ worldwide.

The USA perspective (M Shah, K David, A Evens)

How can you proceed with the diagnostic process?

The constellation of fatigue, fevers, night sweats and anaemia associated with mediastinal lymphadenopathy in a younger patient is concerning for a potential lymphoid malignancy. We would assess for weight loss >10% in the last six months, drenching night sweats, high fevers and pruritus. A thorough physical exam should evaluate for palpable lymphadenopathy, evidence of hepatosplenomegaly, and for extra-nodal involvement. If a palpable node is identified, this may be considered for excisional lymph node biopsy. If not, computed tomography (CT) imaging of the chest with contrast (+/− abdomen/pelvis) for disease localization would be warranted.

Ultimately, excisional lymph node biopsy is the preferred diagnostic procedure of choice. Uncommonly, a core needle biopsy may be considered if the excisional biopsy is not possible due to location of the disease. After tissue diagnosis of classical HL (cHL) has been confirmed, further evaluation should be done such as complete blood count, erythrocyte sedimentation rate, liver and renal function tests, electrolytes, viral studies checking for human immunodeficiency virus (HIV) and possibly hepatitis screening. This should be followed by whole body fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT) scanning for disease staging.[1,2]

Previously, bone marrow biopsy was a standard component of staging; however, with use of FDG-PET/CT, the latter can detect marrow involvement with a sensitivity and specificity of 88–100%.[1] In anticipation of anthracycline and potential bleomycin use, a baseline echocardiogram and pulmonary function tests, respectively, should be obtained. Finally, fertility counselling with options of sperm banking should be provided to this young man given the potential risk, albeit overall low, of azoospermia with therapy.[3]

How would you treat the patient?

With a final diagnosis of cHL with disease location in the mediastinum, bilateral axilla, retroperitoneum and multiple PET-avid parenchymal pulmonary masses, the patient's disease is staged as IVB. Furthermore, his International Prognostic Score (IPS) is +5/7 (i.e., male sex, age, stage IV disease, haemoglobin <10·5 g/dL, absolute lymphocyte count <0·6 × 10^9/l and serum albumin <40 g/l).[4]

Historically, ABVD (doxorubicin, bleomycin, vincristine, dacarbazine) has been a treatment mainstay in North American for advanced-stage HL with an acceptable toxicity profile and

five-year failure-free survival (FFS) and overall survival (OS) rates of 75–80% and 90%, respectively, for patients aged <60 years of age. BEACOPP (bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, prednisone)-based therapy is an alternative strategy that has shown increased acute and potentially longer-term toxicity and improved FFS or progression-free survival (PFS), but without OS benefit in most studies.[5,6]

Recently, FDG-PET/CT-adapted strategies have been examined, including the Response-Adapted Therapy in Hodgkin Lymphoma (RATHL) and S0816 studies.[7,8] Both trials treated all patients with two initial cycles of ABVD. In RATHL, PET2 – patients [Deauville score (DS) of 1–3] were randomized to four more cycles of ABVD vs. AVD (doxorubicin, vinblastine, dacarbazine). Patients with PET2+ (DS 4 or 5) had their treatment intensified to BEACOPP-14 or escalated BEACOPP. In RATHL, 84% of patients had PET2–(16% PET2+). The three-year PFS rate in the ABVD group was 86% vs. 84% [95% consistency index (CI), 80·7–87·5] in the AVD group, which met prespecified criteria for non-inferiority. In the PET2 + group, the three-year PFS was 68%. Interestingly, in an updated analysis with long-term followup of S0816, the five-year PFS for patients with PET2 – disease was only 76%.[9]

An alternative approach is based upon data from the ECHELON-1 trial, which randomized advanced-stage cHL patients to ABVD *versus* doxorubicin, vinblastine, dacarbazine plus brentuximab vedotin (A + AVD) for up to six cycles. This study was not a PET-adapted approach, although PET2 scan was done following cycle 2 of treatment and patients with a DS of 5 could switch to an alternative therapy. The combination of A + AVD resulted in a superior two-year modified PFS of 82% compared with 77% in the ABVD group. Notably, specific subgroups of patients, i.e., those with ≥ 1 extra-nodal site, IPS ≥ 4, stage IV disease, age less than 60 years and male gender, appeared to garner more benefit with A + AVD compared to ABVD.[10] Additionally, patients treated in North America had greater benefit with A + AVD with an absolute two-year PFS improvement of 12% over ABVD. Altogether, given the patients younger age and higher-risk disease including stage IV and high International Prognostic Index (IPI), we would advocate A + AVD therapy for this patient. It is important to highlight that a priori neutrophil growth factor with A + AVD for primary prophylaxis is warranted to prevent neutropenic fever and there should be proactive evaluation for neuropathy.

How would you follow the patient during therapy?

Using the PET adaptive strategy, FDG-PET/CT may be obtained after two or three full cycles of A + AVD therapy. For PET2 – patients, generally four additional cycles of systemic therapy are administered. For those with PET2 + disease (especially DS 5), A + AVD may be continued *versus* change to an alternative therapeutic regimen (e.g., BEACOPP); however, definite benefit of the latter strategy is not proven.

How would you follow the patient at the end of cytoreduction?

For patients with originally bulky disease with a residual PET + lesion >2·5 cm, consolidative radiation therapy (RT) may be considered based in part on the GGSH HD15 study.[11] However, it is not clear if these data may be extrapolated to ABVD-based platforms.

In patients with a strongly positive FDG-PET/CT scan at the end of therapy with suspicion for primary refractory or relapsed disease, biopsy should be performed prior to initiation of salvage therapy. There should also be appreciation of false positivity on FDG-PET/CT and close clinical observation with repeat scanning in two to three months may also be considered. In those with a negative interim and/or end-of-therapy FDG-PET/CT scanning, patients may enter a formal surveillance and survivorship programme. This may include re-staging CT scanning (not FDG-PET/CT) every six months for up to 24 months past the original diagnosis date. There should also be co-existent office visits and consideration for basic blood testing every three months during this time. Routine imaging is rarely warranted beyond 24 months.

How would you address a relapse occurring 18 months after diagnosis?

After first-line therapy, approximately 15–25% of patients will have relapsed or refractory disease, depending on the therapy utilized.[12] It is our strong recommendation to confirm suspected relapse with biopsy. For eligible, fit patients with biopsy-proven relapsed cHL, disease control is optimally achieved with salvage therapy followed by an autologous stem cell transplant (ASCT). The benefits are especially apparent in patients with chemotherapy-sensitive disease, those with early relapse (<12 months), primary refractory disease, presence of poor prognostic markers such as B symptoms and extra-nodal disease.[13,14] A number of salvage regimens are active in relapsed/refractory HL, including ICE (ifosfamide, carboplatin, etoposide), gemcitabine and platinum-based regimens, as well as brentuximab vedotin (BV)-containing regimens, including bendamustine-BV or even BV alone.[15] The goal of salvage therapy should be complete remission of disease prior to ASCT. BV in combination with checkpoint inhibitor therapy has also been reported as tolerable and effective.[16]

Post-ASCT, in patients with high-risk disease such as primary refractory disease, relapse <12 months after first-line therapy or relapse ≥12 months after frontline therapy with extra-nodal disease, we consider maintenance therapy with BV based on the randomized AETHERA study. After ASCT, patients who received upfront BV consolidation had a sustained five-year PFS of 59% and those with at least two risk factors experienced superior PFS [hazard ratio (HR), 0·424; 95% CI 0·302–0·596] compared with placebo.[17] For patients who are transplant-ineligible or progress after an ASCT, checkpoint inhibitor immunotherapy is highly efficacious with an acceptable toxicity profile.

The UK perspective (R Auer, R Ledieu)

How can you proceed with the diagnostic process?

In the UK, it would be usual practice for this patient to be referred into a local hospital on the cancer two-week wait pathway. Once the patient has been seen in the clinic, our approach is to arrange an ultrasound scan of the neck, together with a fine needle aspiration if the lymph node appears pathological on scanning. Following identification of an abnormal lymph node, biopsy is performed. While an excision biopsy remains the gold standard,[18] we, in common with other centres, are increasingly using ultrasound-guided core needle biopsies to expedite the diagnostic process. Blood evaluation including full blood count, erythrocyte

sedimentation rate, renal function, liver function, bone profile, lactate dehydrogenase and testing for HIV takes place. Once the diagnosis of lymphoma has been made, patients are staged by positron emission tomography (PET/CT) scan. We have moved away from routine bone marrow biopsies on patients with advanced-stage disease now that it is generally accepted that PET/CT can accurately detect bone marrow involvement.[19] We offer semen cryopreservation routinely. All investigations would then be reviewed in our multidisciplinary team meeting where formal staging and a treatment plan would be agreed upon.

How would you treat the patient?

Standard treatment in the UK for advanced-stage Hodgkin lymphoma (HL) includes ABVD or escalated BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone).[20] At our centre, we treat patients with six cycles of ABVD, irrespective of Hasenclever/IPS, although many centres in the UK have adopted the practice of escalated BEACOPP for the high-risk patients. Escalated BEACOPP is significantly more toxic without evidence for improvement in overall survival (OS). A number of studies have directly compared the outcomes of patients treated with ABVD *versus* BEACOPP regimens.[6,21–24] The randomized HD2000 study compared six cycles of ABVD, four escalated plus two standard cycles of BEACOPP and six cycles of COPP-EBV-CAD (cyclophosphamide, lomustine, vindesine, melphalan, prednisone, epidoxorubicin, vincristine, procarbazine, vinblastine and bleomycin) in patients with advanced HL.[21] After 10-year follow-up, patients who received BEACOPP experienced better PFS but no better OS against ABVD (PFS 69% vs. 75%; OS 85% vs. 84%). Although BEACOPP affirmed better disease control, this was offset by the increased risk of secondary malignancies in the BEACOPP arm (cumulative risk at 10 years 0·9% vs. 6·6% for ABVD and BEACOPP, respectively).[24] In the Italian cooperative group study, 331 patients with advanced-stage HL were enrolled and randomly assigned to receive six cycles of ABVD or BEACOPP in eight cycles (four courses of the escalated regimen followed by four standard courses). Although the seven-year freedom from progression was significantly higher in the BEACOPP-treated group (85% vs. 73%; $P = 0{\cdot}004$), this did not translate into a survival advantage. This was because patients who progressed following initial ABVD could be ‘rescued’ with salvage with equivalent outcomes to those who received BEACOPP upfront. BEACOPP enthusiasts argue that patients can be cured with “less” treatment, over a shorter time period. However, severe toxic effects are significantly higher with BEACOPP with an increased frequency of acute haematologic adverse events, severe infections and mucositis.[22] This was clearly reiterated in the larger EORTC Intergroup trial where 549 patients with high-risk stage III–IV HL were randomly assigned to eight cycles of ABVD *versus* BEACOPP 4 + 4. Event-free survival (EFS) and OS were similar between the two groups (fouryear EFS 63·7% vs. 69·3%; OS 86·7% and 90·3% for ABVD *versus* BEACOPP, respectively) and toxicity was significantly higher for BEACOPP-treated patients.[6] As a result of the increased immediate and late toxicity observed with the BEACOPP regimens, without a clear survival advantage, we have opted to treat patients with advanced-stage HL with six cycles of ABVD.

How would you follow the patient during therapy?

Following publication of the RATHL trial results,[8] many centres in the UK have moved towards a PET-adapted approach. On trial patients underwent a baseline PET/CT, received two cycles of ABVD followed by an interim PET/CT scan. Patients with a negative scan (defined as DS 1–3) were randomised between continuing with a further four cycles of ABVD *versus* omission of bleomycin (AVD). For patients with a positive scan (DS 4–5) treatment was escalated to BEACOPP. In all, 935 patients had a negative interim PET; 470 were assigned to the ABVD group and 465 were assigned to AVD. ABVD and AVD showed similar efficacy with a three-year PFS rate of 85·7% (95% CI, 82·1–88·6) in the ABVD group and 84·4% (95% CI, 80·7–87·5) in the AVD arm. Patients who continued with bleomycin had more grade 3 or 4 respiratory events. On the basis of this trial, we now de-escalate patients to AVD on the basis of a negative PET scan after two cycles of ABVD.

On the RATHL trial, 182 patients had a positive interim PET and after escalating to BEACOPP the three-year PFS was 67·5%. The South West Oncology Group (SWOG) S0816 study adopted a similar approach whereby patients who were PET + after two cycles of ABVD escalated to BEACOPP. Outcomes were comparable with a two-year PFS of 64% for this patient group.[7] Furthermore, PET2 + patients treated on the Italian HD 0607 followed the same approach with a three-year PFS of 60%.[25] In this study, 150 patients were PET2 + and the majority were reported as DS 4. Patients with DS 5 represented 6% of the study population. Outcomes were significantly different between these two PET2 + groups. In patients with DS of 4 vs. 5, the three-year PFS rate was 73% (95% CI, 62–81%) vs. 35% (95% CI, 22– 49%; $P < 0{\cdot}001$) respectively and the three-year OS rate was 92% (95% CI, 84–96%) vs. 83% (95% CI, 67–92%; $P < 0{\cdot}001$) respectively. This suggests novel treatment approaches are needed for this small high-risk group of patients. The HD0801 took a different approach. Patients who were PET + following an interim PET after two cycles of ABVD (PET2) were escalated to an early ifosfamide-containing salvage treatment followed by stem cell transplantation. PET positivity was defined as DS 3 or more. Thus, 103 of the 512 evaluable patients were PET2 + and among them, 81 received the scheduled salvage regimen with transplantation. Fifteen remained on ABVD as decided by the treating physician, mostly because of minimally positive PET2. Outcomes were excellent in the PET2 + group and very similar to those patients who were PET2– (two-year PFS 76% PET2 + vs. 81% PET2–).[26] For those patients who have DS 5 on an interim PET after two cycles of ABVD, we would plan to perform a repeat biopsy and treat with an ifosfamide-containing salvage regimen followed by autologous stem cell transplant on the basis of the poorer outcomes for this patient group even if treatment is escalated to BEACOPP. For those patients with a DS 4 response on PET2, we have generally continued with ABVD on the basis of a response, albeit more slowly.

How would you follow the patient at the end of cytoreduction?

Following completion of chemotherapy, we perform an end of treatment PET scan six weeks after the last dose of chemotherapy. For those patients who have not achieved a complete metabolic response, we plan for a repeat biopsy. If residual HL is confirmed, the patient is treated with an ifosfamide-containing salvage treatment [IGEV (ifosfamide, gemcitabine, vinorelbine) is our regimen of choice] consolidated by an ASCT. There is a small group of

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patients where radiotherapy is considered, and this decision is made on a case by case basis. For those patients who have achieved a complete response, clinical follow-up continues every three months in the first year, reducing in frequency thereafter. Further scans are only performed on the basis of clinical indication.

How would you address a relapse occurring 18 months after diagnosis?

At point of relapse, it is essential to confirm the presence of HL by repeating a biopsy due to the possibility of a change in histology or alternate non-malignant diagnoses such as sarcoid. Once confirmed, the aim of treatment at this point, in a young fit patient, would be to obtain a PET – complete remission which is then consolidated with an ASCT.[27,28] This approach will be curative in approximately 50% of patients. There are many multiagent chemotherapy salvage regimens with data to support use in relapsed HL. However, these are all single arm phase I studies with no clear advantage of one over another. At our centre, we use IGEV [overall response rate (ORR) 81% and a complete response rate (CRR) of 54%].[29] Equally, there are no data to guide the number of cycles of salvage required. At our centre, the patient would receive two cycles of salvage and then be re-evaluated by PET. If PET– (DS 1–3) following cycle 2, the patient would receive a further cycle of IGEV followed by stem cell harvest. The patient would then proceed directly to a carmustine/lomustine, etoposide, cytarabine and melphalan (BEAM/LEAM)-conditioned autologous stem cell transplant. This is based on data from two randomised studies which demonstrated the significant benefit [albeit in freedom from treatment failure (FFTF), not OS] of ASCT over chemotherapy alone.[14,28] The AETHERA trial demonstrated that early consolidation with BV following ASCT in high-risk patients improved PFS.[30] However, this therapeutic approach is not currently funded in the UK. For those patients who do not achieve a PET – response, a second-line salvage therapy is given because of the poor outcomes associated with nodal disease that remains FDG-PET+.[31,32] In this situation BV is commonly used and it has been shown to act as a non-toxic bridge to ASCT in 34% of relapsed/refractory patients.[33] The PD1 inhibitors nivolumab and pembrolizumab are not currently available to prescribe in the UK in this setting.

The perspective from Germany (S Kreissl, PJ Bröckelmann, P Borchman)

The anamnesis of this 21-year old patient is quite typical for patients diagnosed with HL. With a median age of around 30 years at first diagnosis, HL is one of the most common malignancies in young adults. Most patients present with painless and ongoing, supradiaphragmatic and/or inguinal lymphadenopathy. Approximately 30% of all patients suffer from constitutional symptoms (also called B symptoms) such as fever, night sweats and profound weight loss. HL may also involve extra-nodal sites including the spleen, liver, lungs and bone marrow.

How can you proceed with the diagnostic process?

Upon suspicion of a lymphoma, the histological diagnosis is to be established on the biopsy of a lymph node or of another primarily involved organ. The biopsy should include an entire lymph node, if possible, or a sufficient portion of tissue. Fine needle biopsies are of little diagnostic value as they do not represent the architecture of the lymph node and therefore

often preclude an accurate diagnosis. If the suspected diagnosis of HL is confirmed, the determination of the disease stage and risk group is critical for the choice of initial treatment. Obligatory examinations for an accurate staging comprise clinical symptoms (B symptoms), laboratory diagnostics (including erythrocyte sedimentation rate), contrast-enhanced computed tomography (ceCT) of neck, thorax and abdomen and a bone marrow biopsy unless bone marrow involvement can be excluded by PET.[1] If available, PET-CT is strongly recommended for initial staging. Before the start of systemic treatment, all female patients should discuss preventive measures regarding fertility with a gynaecologist. Male patients should be informed about the possibility of pre-treatment sperm cryoconservation.

How would you treat this patient?

HL is a highly chemotherapy-sensitive malignancy in most cases. However, the choice of the first-line treatment regimen determines the risk of disease relapse.[8,34] More intensive regimens reduce the likelihood of relapse considerably. Available data on the survivors‘ perspective demonstrate that avoiding relapse and being primarily cured from HL is considered the most important aspect in the choice of treatment for the vast majority of patients. Interestingly, most patients are more worried about the risk of relapse and second neoplasia than the risk of death. Additionally, physical, psychological and socio-economic sequelae during follow-up are more frequent among relapsed survivors, as they require further, even more toxic therapies.[35] Therefore, the study end-point, PFS, reflects the patients´ perspective on the most important treatment goal. Accordingly, the current German Hodgkin Study Group (GHSG) standard of care for advanced-stage HL consists of 4–6 cycles of escalated BEACOPP (eBEACOPP; bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone) depending on the early response of the tumour (PET2). With this approach, the prognosis is excellent with five-year PFS and OS rates exceeding 90% and 95%, respectively.[34] In PET2 – patients (i.e. DS < 4), a reduction to only four cycles of eBEACOPP turned out to be non-inferior to six or eight cycles of eBEACOPP in terms of PFS, and even superior in terms of OS. Most notably, treatment-related morbidity was significantly reduced with four cycles of eBEACOPP, a benefit that was observed both for organ toxicity as well as haematological toxicity. In case the patient is PET2+ (i.e. DS ≥ 3), he will receive a total of six cycles of eBEACOPP. Still, acute and long-term toxicities of eBEACOPP remain a matter of concern even with only four cycles. Therefore, the GHSG aims at further improving treatment tolerability while maintaining its excellent efficacy. The ongoing HD21 trial (NCT02661503) evaluates the combination of conventional chemotherapy with BV (BrECADD; BV, etoposide, doxorubicin, cyclophosphamide, dacarbazine, dexamethasone). It aims at a dose reduction of certain conventional cytostatics in order to reduce the rate of adverse effects while maintaining an equally good response to treatment.

How would you follow the patient during therapy?

Apart from the first chemotherapy cycle, for which hospitalization is recommended, the patient will be treated in an outpatient setting. During chemotherapy, safety assessments including blood counts two or three times per week and additional parameters (e.g. creatinine, bilirubin, uric acid) to assess organ function at the end of each cycle will be

performed. Treatment delay or dose reduction strategies are possibilities in case of insufficient or delayed haematologic recovery.

How would you follow the patient at the end of cytoreduction?

In case of PET+, after completion of chemotherapy (DS ≥ 3), the patient will receive local consolidation radiotherapy with 30 Gy. Otherwise, the patient will enter the follow-up period immediately. The patient will be seen for clinical follow-up examinations at regular intervals at least for five years. Routine examinations include a detailed anamnesis, a physical examination, and some instrumental/imaging examinations and laboratory analyses (e.g. pulmonary function tests, echocardiography and thyroid diagnostics). Apart from treatment-related toxicities, impairments in the patient‘s quality of life demand special attention. Cancer-related fatigue (CRF) is among the most frequently observed patient-reported impairments in HL survivors.[36] It is associated with adverse effects on psychological well-being, everyday life including family, work and social participation and presumably on medical treatment adherence as well as increased health care utilization.[37] Routine screening for CRF should be performed so that patients can be offered fatigue-specific interventions such as exercise programs or cognitive-behavioural therapy.[38,39]

How would you address a relapse occurring 18 months after diagnosis?

At first relapse, high-dose chemotherapy (HDCT) and ASCT represents the GHSG standard of care in eligible patients with relapsed HL. After two cycles of salvage chemotherapy [e.g. DHAP (dexamethasone, cytarabine, cisplatin) or ICE], patients are consolidated with BEAM high-dose chemotherapy [BCNU (etoposide, cytarabine, melphalan)] followed by ASCT. With this strategy, up to 50% of patients can be cured.[12,40] High-risk patients have been shown to benefit from tandem HDCT and ASCT when compared with a single ASCT in indirect historic comparison.[41,42] Additionally, a maintenance therapy with BV following ASCT should be considered in case of adverse risk factors.[43] A recently published analysis revealed five easily available clinical risk factors [stage IV, time in therapeutic range (TTR) ≤ 3 months, bulk ≥ 5 cm, Eastern cooperative oncology group (ECOG) ≥ 1 and non-response to salvage, either measured as decreased partial response (PR) by CT or PET+] that allow an accurate and reliable risk stratification for further treatment in patients with relapsed HL.[44]

The perspective from India (A Korula, V Matthews)

In many low and middle income countries (LMIC), medical care costs are predominantly borne by the patients and their extended families[45] and in some cases these costs can drive families below the poverty line.[46] In this setting, translating recent advances in the management of even a highly curable malignancy such as HL into the clinic can be a challenge. In India, a conventional ABVD chemotherapy is relatively affordable ($120 per chemotherapy cycle using generic drugs); however, a single PET/CT scan costs up to $400. With the aim of maintaining excellent outcomes while limiting toxicity, treatment algorithms in HL have evolved based on PET/CT as an imaging modality at diagnosis, interim and final assessments,[1,8] but the universal applicability and relevance of this and other recent advances in management guidelines have not been addressed in the setting of LMIC. In this

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discussion, we focus on the management of patients with advanced HL in a resource-limited setting.

How can you proceed with the diagnostic process?

The treatment and referral pattern seen in this case are typical of many cases we see, where the use of alternative medical care is the norm rather than the exception, due to accessibility and low costs. When ineffective in alleviating symptoms, this is often followed by empirical therapy with antibiotics and anti-tuberculosis therapy (ATT). This patient's performance status was poor by the time he presented to a tertiary care centre for evaluation. He was cachexic, with bilateral bulky cervical lymph nodes, axillary lymph nodes and an enlarged spleen. Our immediate initial evaluation includes a complete blood count, tests for liver and renal function, hepatitis and HIV. We proceed immediately with a cervical lymph node biopsy and make efforts to rule out co-existent infections, notably tuberculosis.[47] The histopathological report shows cHL subtype nodular sclerosis, with no granulomas or any other evidence of infections.

The ideal way to stage this patient is with a PET scan, though a CT scan of the neck, thorax and abdomen would suffice.[1] The patient stated that his family's monthly income is $150, and he does not have a medical or state insurance. He had not been to work for the past six months, and the CT scan alone would cost more than his regular monthly salary. In the face of these financial constraints, we would ask what additional information the CT scan would provide: We know that he has B symptoms, bulk disease, at least stage III disease and basic blood tests indicate an IPS score of 5/8. With the available information it is evident that he has advanced-stage, bulk disease and therefore, regardless of PET/CT scan, would require six cycles of ABVD, followed by involved field radiotherapy (IFRT)to the mediastinal mass. We therefore plan basic staging techniques with a chest Xray, bone marrow examination and an abdominal ultrasonogram, all of which are affordable to this patient.

How would you treat the patient?

In advanced HL, the BEACOPP regimen has been shown to be more effective than ABVD; [48] however, we continue to use six cycles of ABVD in this setting. This approach may be more prudent when resources are a constraint, and there is an increased risk of infection-related morbidity.[49] The economic impact of febrile neutropenia is significant enough to prompt discontinuation of therapy in some cases, with unacceptable morbidity and sometimes mortality in the setting of high rates of multidrug-resistant organisms.[50]

How would you follow the patient during therapy?

The backbone of treatment for HL, ABVD, at 700$ for six cycles, is one of the most affordable regimens available. Recent studies have focused on the de-escalation/escalation approach based on interim PET scans,[8] with the omission of bleomycin after two cycles if the interim PET2 is negative. However, in this specific clinical setting, with a young patient, good lung function, a low risk of bleomycin toxicity and most importantly limited finances, an interim PET is not practical. We plan for six cycles of ABVD in this patient, without considering de-escalation. We do ask for a history of cough or breathlessness and examine the respiratory system prior to each dose of bleomycin. Only in case of a suspicious history

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or abnormal findings is pulmonary function testing/high-resolution CT performed, and bleomycin subsequently omitted.

How would you follow the patient at the end of cytoreduction?

At the end-of-therapy assessment, a PET scan is ideal, but in the resource-limited setting, a CT scan is done for the purpose of planning consolidation radiotherapy. If radiotherapy was not part of the initial treatment plan (no bulk disease), then end assessment may consist of clinical examination and basic imaging with chest X-ray/abdominal ultrasonogram. With this approach, limiting PET scans to patients who are able to afford them, and using basic techniques for those unable to afford PET scan, we have shown almost equivalent outcomes in these two groups of patients.[51] The only factor adversely affecting outcome in HL with the use of ABVD was the presence of advanced-stage disease. If in remission, the patient is asked to follow up with basic blood investigations and a full clinical examination every six months for five years. We do not subject the patient to re-imaging unless he is symptomatic.

How would you address a relapse occurring 18 months after diagnosis?

In case of a clinical relapse, we re-biopsy the lesion, and then counsel the patient on the costs involved. With changing practice and the introduction of the GCD (gemcitabine, carboplatin, dexamethasone) regimen, cytopenia is minimal, alleviating the need for in-patient therapy in the majority of cases, therefore significantly decreasing the cost of therapy compared to DHAP.[52] Following salvage therapy and assuming an adequate remission, autologous transplant costs are approximately $6000. As the number of patients with relapsed disease are far fewer than newly diagnosed HL, we are often able to raise funds from both governmental and non-governmental agencies for many patients to proceed with an autologous transplant.

If the patient does not respond to the first line of salvage therapy, and is unable to finance further chemotherapy (either conventional or novel agents), in most cases, we would then consider palliation with an oral chemotherapy regimen like COPP (cyclophosphamide, vincristine, procarbazine, prednisone). In rare cases, we have even had patients on the COPP regimen return for re-assessment, in remission, and have proceeded with autologous transplant, and therefore would not hesitate to try this as a last attempt.

Treating malignancy in LMIC is wrought with challenges, however HL remains one of the most eminently treatable cancers, even with limited resources. The key to optimal management is correctly assessing the patient’s ability to bear treatment costs, and tailoring therapy to address these needs. With the most basic staging tools and chemotherapy regimens, treating HL remains one of the satisfying aspects of haemato-oncology.

The perspective from Thailand (W Owattanapanich)

How can you proceed with the diagnostic process?

This patient is referred for evaluation of mediastinal mass, suspected to be advanced cancer. The initial laboratory evaluation should include complete blood count (CBC) and peripheral blood smear (PBS) as T-ALL (acute lymphoblastic leukaemia) is one of the differential

diagnoses that can be diagnosed immediately from the presence of unexpected blast cells in peripheral blood. As with lymphoma, CBC and PBS might reveal cytopenia or a leucoerythroblastic blood picture that reflects lymphomatous involvement of the bone marrow. Subsequently, bone marrow aspiration, routinely performed by haematologists in Thailand, is warranted to appreciate the morphology of the lymphoma or leukaemic cell, taking only a few hours to get the result. In addition, the bone marrow biopsy is also sent to a pathologist to perform further immunohistochemistry studies. Apart from haematologic malignancies, germ cell tumour is supposed to be included in the differential diagnosis. These can be readily diagnosed by obtaining a few blood works. Therefore, measurements of serum lactate dehydrogenase (LDH), serum β-human chorionic gonadotropin (HCG) and α-fetoprotein are also of value.

If the diagnosis cannot be made by the previous tests, computed tomography (CT)-guided biopsy of the mediastinal mass performed by a radio-interventionist should be done to help making a definite diagnosis. Consulting a pathologist is also important to get the results in a timely manner. Lymph node imprint is usually done for initial evaluation by the haematologist. If the preliminary result is consistent with lymphoma, corticosteroid would be utilized to relieve the clinical symptoms of superior vena cava (SVC) syndrome. The more detailed investigation for prechemotherapy evaluation includes blood chemistry profiles, viral serology, echocardiography, pulmonary function test and dental examination. Once the diagnosis of lymphoma has been made, specific treatment should promptly be given. Tumour lysis work-up and prevention should be done afterward. CT with contrast is utilizedfor staging in most patients according to the Thai healthcare system. PET/CT can be performed in a small percentage of patients who can afford the extra cost of approximately 500 euros.

Back to our patient who, finally, is diagnosed with Hodgkin lymphoma stage IV, categorized as advanced-stage group. The decision on which specific treatment regimen should be administered is made according to the Thai lymphoma study group guidelines, relying on IPS score and age. His IPS score is at least four points due to male sex, stage IV, hypoalbuminaemia and anaemia. Escalated BEACOPP is preferred over ABVD due to the improvement in outcome when using this regimen in this group of patients. Unfortunately, procarbazine is not available in Thailand. The escalated BEACODD regimen has been used instead, replacing procarbazine by dacarbazine and prednisolone by dexamethasone. This regimen is given at a 28-day-interval and consists of 10 mg/m^2/day of bleomycin intravenously on day 8, 200 mg/m^2/day of etoposide on days 1–3 intravenously, 35 mg/m^2/day of doxorubicin on day 1 intravenously, 1250 mg/m^2/day of cyclophosphamide on day 1 intravenously, 1·4 mg/m^2/day of vincristine on day 8 intravenously, 40 mg/m^2/day of dexamethasone on days 1–4 orally and 250 mg/m^2/day of dacarbazine on days 2–3 intravenously. Moreover, baseline BEACODD can be used following escalated BEACODD if a good response is achieved. Compared to escalated BEACODD, the dosage of etoposide, doxorubicin and cyclophosphamide is reduced to 100 mg/m^2/day, 25 mg/m^2/day and 650 mg/m^2/day, respectively, in baseline BEACODD. Evaluation of the efficacy and toxicity of this regimen is ongoing.

How would you follow the patient during therapy?

After four cycles of escalated BEACODD, a CT scan with contrast is requested for response evaluation. If the patient achieves complete response, another four cycles of baseline BEACODD with additional involved site radiation therapy (ISRT) at the end of chemotherapy is recommended. If a PR can be attained, two cycles of escalated BEACODD followed by ISRT is suggested. Lastly, if no response is seen, the patient will be treated as refractory.

How would you follow the patient at the end of cytoreduction?

After the completion of treatment, a long-term follow-up for monitoring of relapse and side effects of treatment is mandatory, including interim complete history, physical examination, CBC and erythrocyte sedimentation rate (ESR) every three months for one year, then every six months until year 3 then annually, annual thyroid-stimulating hormone in patients receiving radiotherapy for neck, annual fasting blood sugar and lipid profile after five years post-therapy, annual breast screening initiating 8–10 years post-therapy or at age 40 if patients underwent chest or axillary radiation, stress test/echocardiogram at 10-year intervals after treatment is completed and carotid ultrasound at 10-year intervals if neck irradiation was done. Annual influenza vaccination is recommended. Additional vaccines such as pneumococcal, meningococcal and *Haemophilus influenzae* vaccine are offered in patients treated with splenic radiation or previous splenectomy. Interval CT scan with contrast is also not routinely done and is indicated only for clinically suspected of relapse disease.

How would you address a relapse occurring 18 months after diagnosis?

If relapse occurs within 18 months after making a diagnosis, a number of salvage regimen options can be delivered depending on each institute's preference and the patient's reimbursement programme. Generally, for universal healthcare coverage schemes, ICE, ESHAP (etoposide, methylprednisolone; cytarabine, cisplatin) and DHAP regimens can be used according to standard recommendations[53,54] If the price is affordable for the patient, GVD (gemcitabine, vinorelbine and dacarbazine), IGEVand BeGEV (bendamustine, gemcitabine and vinorelbine) regimens are also available in Thailand. These relapsed patients should proceed on stem cell collection after their disease status has improved and at least PR to chemotherapy is announced. High-dose therapy with stem cell rescue is the major goal of patients at first relapse.[55] However, the number of hospitals that have facilities to perform stem cell transplantation is limited. Accordingly, only a fraction of relapsed patients can undergo autologous stem cell transplantation. BVis preferable for maintenance therapy after transplantation in a high-risk group of patients having a post-transplantation relapse based on the phase 3 AETHERA trial with patients who are refractory to frontline therapy, with relapse < 12 months after frontline therapy and relapse ≥ 12 months after frontline therapy with extra-nodal disease.[17] Again, BV is costly and is not included in the Thai universal healthcare system.

Discussion (J Trotman, Australia)

Diagnostic work-up

This young man presents with cervical lymphadenopathy and systemic “B” symptoms, necessitating a diagnostic work-up to exclude infection and characterise a likely lymphoma. Our North American colleagues highlight the importance of an excisional biopsy, and I emphasise the merits of a close relationship with surgical colleagues as part of a multi-disciplinary team, who can facilitate excisional biopsies. The fine needle aspiration followed by ultrasound guided core biopsy approach described by our British colleagues may be as much a reflection of potential resource limitations as it is on expediting the diagnostic process. Nonetheless, should core biopsies be performed, the radiologists should be well educated about the importance of at least three to four cores for histology as well as a fine needle aspirate for flow cytometry. While the diagnosis of Hodgkin Lymphoma is a lot easier in the presence of Reed-Sternberg cells these can be sparse and a good tissue sample is important to distinguish Hodgkin from grey zone and primary mediastinal lymphomas, which are also of more common in this age group.

Shared decision making

The five global treatment recommendations highlight the common protocol-based national or institutional approaches that currently exist in the treatment of advanced stage Hodgkin lymphoma. Such approaches bring inherent risks of physicians’/institution’s own treatment bias disproportionately impacting on therapeutic decision-making. Analysis of the relative merits of any approach should be conducted by presenting a comprehensive patient summary, including pathology, imaging and patient preferences, for peer review in a multidisciplinary team setting, both at diagnosis and for response assessment. Where multidisciplinary review is not available, discussion with at least one other colleague, knowledgeable in the management of Hodgkin lymphoma and the healthcare environment of the patient is desirable in any setting. Most importantly, treatment decisions should be made in partnership with the patient after an exploration, during the diagnostic consultations, of the patient’s priorities, and their social and financial health care circumstances. I would like to identify the adequacy of his spermatogenesis and availability of cryopreservation: the availability of retrieval techniques for spermatozoa in the event of azoospermia is of relevance, especially if planning an escalated BEACOPP approach. Given the myriad of patient, disease and health system factors to consider, for some patients a fully-shared decision-making approach is too overwhelming, but many patients are capable of assessing for themselves the trade-offs between projected time to completion of therapy, acute and late toxicities, fertility preservation, the burden of future fertility measures, progression free and ultimately overall survival. “Soft institutional paternalism” in Haematology is increasingly inappropriate in the modern era.

PET-adapted approaches

I concur with a PET-adapted approach recommended by most contributors. The key challenge is choosing either an escalated or a de-escalated chemotherapy approach for a given patient.

In the Response Adapted Therapy in Hodgkin lymphoma (RATHL) study,[8] examining the omission of bleomycin after two cycles of ABVD in patients achieving PET-negativity, and the change to escalated BEACOPP or BEACOPP14 in patients remaining PET-positive, the 5-year PFS for the 56% of patients ≤35 years was 84% (80–86%) and the 5-year OS was 97% (96–98%). The primary endpoint of non-inferiority of omission of bleomycin in cycles three to six of A(B)VD was met.[56] However, even in the 84% of patients who achieved PET-negativity there was a 4% inferior 3-year OS in patients with either advanced stage or high IPS. Overall 5-year PFS in the RATHL study was 80% (77–82%) and 5-year OS 94% (92–95%). On this basis, I endorse my US, UK and Indian (where the patient has the resources to pay for a single interim PET after 2 cycles), colleagues' adoption of the RATHL approach if commencing treatment with ABVD for this man. Notwithstanding this recommendation, clinicians in resource constrained settings where even a single PET-CT is not possible will be reassured by the comparable relapse free survival rate in patients receiving ABVD with suboptimal imaging analysis, as recently reported in this journal.[57]

Alternatively, while there is no clear OS difference, the cumulative data supports a PFS advantage if commencing treatment with escalated BEACOPP. The German Hodgkin Study Group (GHSG) HD18 study[34] provides an excellent PET-adapted approach, potentially limiting the escalated BEACOPP exposure to only 4 cycles in the 52% of patients who achieve PET-2 negativity. In this study, the 5-year PFS is 89% (88–91%), with a 5-year OS estimate of 96% (95–97%). Indeed, with a median 4–10 years follow-up in all studies cited we can only provide OS estimates with any certainty until this man is 30 years old. The German data re. prioritisation of PFS, not OS, as the most important goal does require prospective validation of a balanced population of patients commencing either ABVD or escalated BEACOPP.[35] Any analysis of patient preferences will always be biased by that of their treating clinician, the gatekeeper to most but not all information in this digital era. Patient preferences may undergo a shift during survivorship follow-up, and also in an environment of rapid therapeutic advances, particularly in salvage therapies. I note the German recommendation for in-patient care during cycle one, which may present a. logistical challenge, even in advanced health care systems. They also recommend intensive management of cancer related fatigue after escalated BEACOPP. Furthermore, the rate of radiotherapy use after escalated BEACOPP is notable: 36% of the 48% of patients who remained PET-2 positive in HD18[34] had residual PET-positive lesions, and underwent 30 Gy consolidative radiotherapy. With significant short and long-term toxicity of this regimen the German-led randomised HD21 study, (NCT02661503), examining the efficacy of a BRECADD vs. escalated BEACOPP PET-adapted approach is timely.

I caution against cross-study comparisons of an ABVD vs. escalated BEACOPP PET-adapted approach, i.e. between the RATHL8,[56] and HD18[34] studies. In RATHL, while the study included a higher proportion of patients with poor risk early stage disease, it also enrolled a higher proportion of older patients: almost 20% of patients were aged ≥50 years and 10% were above the 60-year age limit applied in HD18. With a median 4·3 years of follow-up, the HR for death in patients ≥50 was 5·3 (95% CI 3·3–8·6). Enrolment of patients aged up to 79 years was based on the low probability of needing to deliver an escalated BEACOPP approach. The recently published AHL2011 study demonstrated non-inferiority of a PET-based de-escalation after two cycles of escalated BEACOPP. The 84% of patients

who achieved PET-negative status proceeded to two additional cycles of ABVD followed by a second interim PET which if negative was followed by two further ABVD. This response-adapted approach based on two interim PET scans resulted in reduced toxicity without impairing five-year disease control.[59] A recent cost-effective modelling of treatment of advanced HL identified the AHL2011 study as providing the most quality-adjusted costeffective approach, except when fertility preservation is important and the RATHL approach is preferred.[60]

When utilising a PET-adapted approach, the clinician must also be mindful of the PET criteria of the reference study; specifically, the definition of interim-PET positivity. In HD18 a Deauville Score (DS) of ≥3 (i.e. FDG uptake higher than mediastinum) defined PET-positivity in 48% of randomised patients, whereas the DS of ≥4 (i.e. FDG uptake moderately higher than the liver) was the cut-off to identify the 16% interim-PET-positive patients in the RATHL study. Similarly, if the A + AVD approach is made I encourage my American colleagues to adhere to the ECHELON-2 protocol 10 and utilise a PET-adapted strategy after 2, not 3 cycles of A + AVD. Nonetheless, in my opinion, the trade-off, between the 5% 2-year modified PFS advantage and its clinical toxicity and financial burden, does not warrant substituting brentuximab vedotin for bleomycin.

Low resource environments

Recognising the significant acute and long-term toxicity of escalated BEACOPP I agree it is neither feasible, nor appropriate, to deliver in LMIC countries, with a gross national income <$3895 USD per capita.[58] Our Indian colleagues are faced with both limited access to inpatient care and supportive granulocyte colony-stimulating factor, as well as widespread antibiotic resistance. Their pragmatic approach to staging with CXR, BM biopsy and abdominal ultrasound, and utilisation of 6 cycles of ABVD for this man represents value-based health care in a resource constrained setting.

In Thailand, where universal health care coverage does not extend to PET imaging and procarbazine is unavailable, the BEACODD adaptation of Esc BEACOPP may seem a pragmatic solution, but it is one without an evidence base. The substitution of dacarbazine echoes the current GHSG HD21 study aiming to avoid the secondary malignancy and gonadal toxicity of procarbazine. Likewise, the substantial reduction in the steroids from 14-day prednisone therapy to 4-days of dexamethasone may reduce the rate of avascular necrosis reported with escalated BEACOPP. There is no precedent for prolonging cycle duration from 21 to 28 days. It could be argued that translating the data from the GHSG HD15 trial,[11] a patient achieving CT-based CR with the escalated BEACODD regimen need only complete two further cycles of escalated BEACODD. In patients with a residual lesion> 2·5 cm, for whom a single post-induction PET is affordable, it will identify the estimated 11% of study patients likely to benefit from 30Gy radiotherapy.

Remission follow-up

Consensus guidelines advise, that outside of clinical trials, there is no justification for the unnecessary expense and anxiety to patients from routine CT surveillance scanning, nor is there evidence to support a role for surveillance PET-imaging.[1] More important is a focus on

survivorship issues for this man: addressing fatigue and fertility, implementing smoking cessation and weight management programs if necessary, optimising cardiovascular, thyroid and dental health, as well as psychologic support over any fears of relapse.

Relapse

Finally, in the setting of relapsed disease, the general principles of biopsy confirmation, and 2–3 cycles of salvage chemotherapy followed by ASCT consolidation are well documented and universal. However, identifying an OS advantage of any therapeutic approach becomes of even greater importance in the relapsed setting. In the absence of such I do not support the use of brentuximab vedotin consolidation after transplantation.[17]

Conclusion

The medical literature (and social media) energetically debate the merits of a PET-adapted escalation or de-escalation approach in the first-line management of Hodgkin lymphoma. The German philosophy in the treatment of advanced stage disease is to use a PET-adapted escalated BEACOPP approach, adopting the ancient philosopher Kairos' principles of "seizing the moment" and" timeliness of therapy". However, when reflecting on the Kairos principle, Aristotle stated "each rhetorical situation is different and therefore different rhetorical devices need to be applied at that point in time".[61] The social circumstances and health care environment within which this young man is diagnosed is such a rhetorical situation. Truly patient-centred care requires the clinician to develop a clear understanding of this young man's health (including spermatogenesis) and social context and local health care resources. It requires us to invest time in his education and explore his own treatment preferences, before embarking on any therapeutic approach, ideally a PET-adapted one, where affordable.

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Box 1

Case story A 21-year-old male has been feeling more and more fatigued over the last four weeks. During the last two, he has been experiencing night sweats and shortness of breath. His girlfriend has found swellings on his neck. A visit to his GP resulted in blood sampling, which showed anaemia and decreased albumin levels. A chest X-ray revealed pronounced mediastinal gland swelling and a diffuse parenchymatous affection. The patient is referred to a secondary centre for evaluation on the suspicion of advanced cancer.

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Table I

Approaches to the diagnosis and treatment of advanced Hodgkin's disease

	Diagnosis	Initial therapy	Follow-up during therapy	Follow-up after therapy	Relapse management	Remarks
USA	PET scan, PFTs with DLCO (if using bleomycin) and echo (and fertility preservation); no bone marrow, unless for patients over age of 60– 65 years and with cytopenias	Younger pts ages < 60–65 years: A + AVD for IPS 3-7; RATHL based therapy for IPS 0–2 pts ages> 60–65 years who are fit: sequential BV and AVD; for unfit: brentuximab vedotin ± DTIC	Repeat PET s/p 3 cycles; once negative, then CTs	Office visits q 3 months and re-staging CT scans q 6 months for 2 years (starting counting from diagnosis)	Transplant-eligible: ICE if relapse < 1 year vs. Brentuximab vedotin if relapse> 1 year followed by ASCT; BV maintenance after transplant if> 2 risk factors Transplant-ineligible: BV ± PD1 inhibitor (unless resistant to the former-then PD1 inhibitor alone)	Always advocate participation in a clinical trial
UK	Excision biopsy is the gold standard; however, core biopsies are increasingly used to expedite the diagnostic process	PET-adapted. ABVD. escBEACOPP is used by some centres for high-risk patients	PET2 response: For PET-patients (DS1–3) then AVD × 4 For PET+ patients (DS 4 or 5) some centres in UK escalate to escBEACOPP. Alternatively ifosfamidecontaining salvage for DS5 patients followed by ASCT in those patients who respond	End of treatment PET scan 6 weeks after the last dose chemotherapy	Re-biopsy Ifosfamide-containing salvage followed by ASCT for patients who are PET– (DS 1–3) after salvage For PET+ patients after 2 cycles of salvage, second-line salvage – BV	ABVD is the regimen of choice. DS 5 patients on PET2 are escalated to IGEV. DS 4 patients generally continue on ABVD The preferred salvage at Barts is IGEV
Germany	Histological diagnosis, preferably on excisional biopsy Assessment of disease extent and risk factors by PET Discuss measures to preserve fertility	Within a clinical trial if available (eg GHSG HD21) PET2-guided 4–6 cycles of eBEACOPP outside a clinical trial	Consider in-patient administration of the first escBEACOPP cycle Laboratory safety assessments 2-39/week. Dose delay and/or reduction in case of prolonged haematologic recovery	Consolidative RT with 30 Gy to PET+ (DS ≥ 3) residues Regular follow-up visits at increasing intervals for the first 5 years Focused on treatment-related toxicities and cancer-related fatigue	Salvage chemotherapy with eg 2 cycles DHAP followed by BEAM and ASCT. Consider tandem ASCT and/or consolidation with BV in higher-risk patients	
India	Open biopsy wherever feasible, otherwise a trucut biopsy adequate for histopathology and immunohistochemistry Staging with resource constraints: clinical examination, ultrasound abdomen, chest X-ray and bone marrow biopsy Staging – No resource constraints: whole body PET/CT scan	Resource constraints: ABVD 6 cycles regardless of stage No resource constraints: ABVD 9 × 6 with plan for interim PET2	Resource constraints: Interim assessment with clinical examination, ultrasound and chest Xray, depending on site of initial disease No resource constraints: Omit further bleomycin if interim PET2–	Resource constraints: IFRT to sites of initial bulk disease Clinical follow-up every 3 months No resource constraints: IFRT to sites of initial bulk disease or PET + lesions> 1·5 cm Clinical follow-up every 3 months	2–4 cycles of GCD followed by autologous transplant in 2nd remission	Our previously published data (Korula et al. Br J Haem 2019) indicates that in a resource constraint setting, using 6 cycles of ABVD without interim or end-therapy PET assessment is a strategy with acceptable disease-free survival rates (3 yr RFS in early stage and advanced stage 88·1% and 73·9% respectively) comparable to CT/PET re-assessment (3 yr RFS 91·8% and 81·3% in early and

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	Diagnosis	Initial therapy	Follow-up during therapy	Follow-up after therapy	Relapse management	Remarks
						advanced stage respectively) - toxicity notwithstanding
Thailand	CT-guided biopsy of the mediastinal mass	Escalated BEACODD regimen followed by ISRT	CT scan with contrast	Complete history, physical examination, CBC and ESR every 3 months for 1 year, then every 6 months until year 3 then annually, annual thyroid-stimulating hormone in patients receiving radiotherapy for neck, annual fasting blood sugar and lipid profile after 5 years post-therapy, annual breast screening initiating 8–10 years post-therapy or at age 40 if patients underwent chest or axillary radiation, stress test/ echocardiogram at 10-year interval after treatment is completed and carotid ultrasound at 10-year intervals if neck irradiation was done	ICE, ESHAP or DHAP regimens and subsequently with ASCT	-A PET/CT can be performed in a small percentage of patients who can afford extra charge. Procarbazine is not available in Thailand. Hence, escalated BEACODD regimen has been used instead, replacing procarbazine by dacarbazine and prednisolone by dexamethasone

A + AVD, doxorubicin, vinblastine, dacarbazine plus brentuximab vedotin; ABVD, doxorubicin, bleomycin, vincristine, dacarbazine; ASCT, autologous stem cell transplant; AVD, doxorubicin, vinblastine, dacarbazine; BEACODD, bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, dacarbazine, dexamethasone; BEACOPP, bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, prednisone; BEAM, carmustine/, etoposide, cytarabine and melphalan; BV, brentuximab vedotin; CBC, complete blood count; CT, computed tomography; DHAP, dexamethasone, cytarabine, cisplatin; DLCO, diffusing capacity of the lungs for carbon monoxide; DS, Deauville score; DTIC, dacarbazine; ESHAP, etoposide, methylprednisolone; cytarabine, cisplatin; ESR, erythrocyte sedimentation rate; GHSG, German Hodgkin Study Group; ICE, ifosfamide, carboplatin, etoposide; IFRT, involved field radiotherapy; IGEV, ifosfamide, gemcitabine, vinorelbine; IPS, International Prognostic Score; ISRT, involved site radiation therapy; PET, positron emission topography; PFT, pulmonary function test; RATHL, Response-Adapted Therapy in Hodgkin lymphoma; RFS, relapse-free survival; RT, radiotherapy.