Navigating increasingly individualised Hodgkin lymphoma treatments to optimally balance risks and benefits

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Commentary on: Follows GA, et al. Guideline for the first-line management of Classical Hodgkin Lymphoma — A British Society for Haematology guideline. Br J Haematol. 2022;197:558-572.

Nearly 80 years after the first reports of curative treatment with radiotherapy (RT) and cytostatic agents, the therapeutic landscape of classical Hodgkin lymphoma (HL) has evolved dramatically. Multi-agent chemotherapy and RT for decades have remained mainstay of HL therapy and provided cure to the majority of patients. However, these conventional treatments come at the price of significant short- and long-term morbidity, with consequences eventually superseding HL-related morbidity and mortality.1,2 These observations have led to unparalleled efforts by the international scientific community and large study groups around the globe continuing to reshape therapeutic approaches in this curable disease. The updated British Society of Haematology (BSH) guideline provides a concise summary of the currently available evidence for the varying approaches in the management of HL patients after first diagnosis. Follows et al.3 provide a framework to successfully navigate the increasingly individualised treatment strategies in both early- and advanced-stage HL.

Today, ~90% of patients with early-stage disease are cured with two cycles of doxorubicin, bleomycin, vinblastine and dacarbazine (2 × ABVD) and 20 Gy involved-site (IS)-RT.4 To date, three large randomised phase III trials have shown inferior progression-free survival (PFS) if RT is omitted in patients achieving a metabolic remission by positron emission tomography (PET, defined as Deauville score [DS] of 1–3) after 2–3 × ABVD.5–7 The authors of the updated BSH guideline adequately discuss the data and generally recommend combined modality treatment for early-stage favourable disease with the possibility to replace RT with +1–2 × ABVD only in selected cases after weighing risks and benefits in a multidisciplinary team. As long-term outcomes are excellent after 2 × ABVD + 20 Gy RT,4 the recommendation and supposed benefit of adding a third ABVD cycle for these patients is however questionable. Importantly, an intensified approach with two cycles of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisolone (2 × eBEACOPP) + 30 Gy IS-RT is recommended in case of PET-positivity after 2 × ABVD for these patients.6

In contrast, omission of RT in the case of a PET-negative remission after intensified chemotherapy with 2 × eBEACOPP + 2 × ABVD (‘2 + 2’) proved to be non-inferior in the recent international German Hodgkin Study Group (GHSG) HD17 phase III trial in the early-stage unfavourable-risk group (which, in accordance with the BSH authors, will be termed intermediate-risk group from hereon).8 While failing to meet the primary end-point assumptions, the European Organisation for the Research and Treatment of Cancer (EORTC) H10U trial showed only very small PFS and no overall survival (OS) differences in intermediate-risk patients when consolidating a PET-negative remission after 2 × ABVD with +4 × ABVD instead of 30 Gy involved-field (IF)-RT.9 Based on these data, the updated BSH guideline considers ‘2 + 2’ or PET-guided ABVD as per EORTC H10U as two possible standards of care with the aim to omit consolidative RT in PET-negative patients. In patients where RT-associated consequences are of lesser concern,
4 × ABVD + 30 Gy IS-RT are recommended. Extrapolating from the randomised Response Adapted Therapy for Hodgkin Lymphoma (RATHL) trial in advanced-stage disease, the authors recommend dropping bleomycin in both early stage favourable- and intermediate-risk patients in case of a negative interim PET (i.e. treatment continued with AVD after >2 × ABVD). Comparable to early stage favourable disease, intensified treatment with +2 × eBEACOPP +30 Gy IS-RT is recommended for patients with a positive PET after two initial cycles of ABVD.

In advanced stage disease, the authors recommend a PET-2-guided approach with either 4–6 × eBEACOPP (GHSG HD18),9 2 × BEACOPP plus 4 × eBEACOPP or 4 × ABVD (AHL2019)10 or 2 × ABVD plus 4 × ABVD or 4 × AVD (RATHL),11 each with 30 Gy RT only administered to PET-positive residues. However, the prognostic impact of PET seems to be dependent on the initial treatment regimen. The 3-year PFS for PET-negative patients after 2 × ABVD in the RATHL trial was only 85%; however, it was 95% for patients in the GHSG HD18 trial after 2 × eBEACOPP. While caution is warranted for cross-trial comparisons, these differences indicate the need for careful development of response-adapted therapies in light of varying therapeutic strategies and sequences. While the authors acknowledge the superior efficacy of eBEACOPP-based approaches, they recommend basing a decision between these treatment strategies on patients’ preferences and fitness. Importantly, the authors recommend fertility counselling/preservation ‘where appropriate’. Today, we have knowledge on the appropriateness of fertility preservation, especially in women: Gonadotoxic effects of both ABVD and eBEACOPP have been shown to be highly dependent on age. Accordingly, women aged >30 years may have relevant gonadal damage from ABVD, whereas young women usually recover from eBEACOPP.12,13 Cryopreservation of oocytes should thus be standard of care for all women who wish for motherhood after the age of 30 years regardless of the chemotherapy chosen. To limit infertility due to procarbazine exposure, the authors consider replacing this drug with dacarbazine (BEACOPPdac) feasible. In addition to these rather thoroughly studied first-line approaches, the updated guideline provides a well-balanced discussion and helpful recommendations towards special situations such as older patients, who should be treated according to fitness and frailty based on formal scoring systems, teenagers and young adults, HL in pregnancy or practicalities for RT, PET, and care beyond lymphoma during follow-up.

As previously outlined and also depicted by the flow charts in the BSH guideline, first-line treatment of HL is already individualised and today largely guided by historically established baseline clinical risk factors and interim PET measured by DS. Given the high overall treatment success rate further individualisation to optimally balance risks and benefits is desirable. By incorporating patient-associated factors such as age, sex, comorbidities, and preferences with disease localisation and spread, as well as more sophisticated biomarkers such as circulating tumour DNA14 or metabolic tumour volume,15 both at baseline and on treatment, modern HL treatment truly tailored to each individual patient is achievable. By accurately determining individual risk of treatment failure and treatment-related side-effects, such approaches would allow further reduction of intensity while adequately addressing the remaining high-risk patients to prevent refractory disease.

To that end, it will be crucial to rigorously assess the interplay of these markers and examine their predictive potential, especially in the setting of the rapidly emerging class of anti-programmed cell death-protein 1-directed immune checkpoint inhibitors (ICI). ICI are highly effective in classical HL and already investigated as first-line treatment16 but associated with distinct response patterns by PET.17 The arising ambiguities pose a potential challenge towards individualised ICI treatment solely guided by PET reported with DS. By addressing these issues, thoughtfully utilising the ever-increasing toolbox of potential biomarkers will allow further individualisation of HL treatment and mark the beginning of a new era in caring for patients with HL.

CONFLICT OF INTEREST
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