Current Treatment Paradigms for Advanced Stage Hodgkin Lymphoma

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Summary

The treatment of advanced classical Hodgkin Lymphoma (cHL) has evolved over the last 50 years with a progressive improvement in long term cure rates in patients up to the age of 60. However, a minority of these survivors experience severe morbidity and mortality resulting from intensive chemotherapy and radiotherapy, leading to a drive to de-escalate treatment without compromising survival. The early identification of patients with chemoresistant disease by functional imaging allows the modulation of therapy and an efficient means to test new agents in those most in need of more effective therapy. The outcomes of treatment for older patients have not improved at the same rate, and this group requires a different approach, incorporating specialist geriatric support to personalise therapy. Clinical trials that focus on quality of life, comorbidity and survival are needed to improve survival rates for this expanding population with complex needs.

Key words: Advanced Hodgkin Lymphoma; Response Adapted Therapy; FDG-PET; Brentuximab Vedotin; Immune Checkpoint Inhibitors; Elderly Patients

Introduction

Classical Hodgkin Lymphoma is a malignancy of germinal centre B cells, characterised by the pathognomonic Hodgkin and Reed-Sternburg cells which have lost their normal B cell surface markers. In contrast to other B cell lymphomas, the tumour microenvironment is composed primarily of immune effector cells including cytotoxic T Cells and Tumour Associated Macrophages (TAMs) with a low abundance of malignant B-cells. Alterations in signaling pathways, major histocompatibility complex (MHC) expression and epigenetic silencing all play a role in pathogenesis, as may the presence of Epstein-Barr virus in a proportion of cases.

The incidence of cHL is estimated at 70,000 cases per year across the world, peaking in the 2nd and 7th decades, and is the most common lymphoid malignancy diagnosed in young adults and children in developed countries (CRUK 2017). The challenge in treating younger patients is to minimise toxicities, including infertility, cardiomyopathy, pulmonary fibrosis and secondary malignancies whilst optimising cure rates. For the older population (in cHL, defined as patients older than 60 years) a different approach is needed, and the use of specific tools and geriatric medical support are important to inform treatment decisions regarding tolerability, quality of life and disease control, with acute toxicity a more dominant consideration than late effects.

In this review we discuss the recent advances in treatment for patients with advanced cHL (defined as Ann Arbour classification Stage IIB to IV) and the challenges that remain, including risk and response adapted treatment approaches, the use of consolidation radiotherapy and how newer antibody-drug conjugates or immune checkpoint inhibitors may help to address some of the areas in which we have previously been less successful.

Initial therapy in Younger Patients

How to decide the optimal intensity of initial chemotherapy?

The use of intensive chemotherapy regimens such escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisolone (eBEACOPP) has led to high cure rates, with excellent disease control and long term survivorship in patients with advanced cHL (Borchmann P *et.al*, 2018). However, the benefits of more intensive initial therapy are offset by an increased incidence of short and long-term toxicity, when compared to other less intensive regimens such as doxorubicin, vinblastine, bleomycin and dacarbazine (ABVD). Treatment-related acute myeloid leukaemia and myelodysplastic syndrome (tAML/tMDS) carry a poor prognosis, occuring between 2-8 years following treatment for cHL,

with the highest incidence in those patients receiving intensive alkylating agents and topoisomerase II inhibitors. The 10 year cumulative incidence of tAML/tMDS in patients receiving eBEACOPP in the German Hodgkin Study Group (GHSG) HD9 trial is estimated at 6-7% (Engert A *et.al,* 2009). This is comparable to the Italian HD2000 study that demonstrated a difference in the 10 year cumulative incidence of second malignancies in patients receiving 6 ABVD or 4 eBEACOPP of 0.7% versus 6.6% respectively, although with the more recent use of reduced number of BEACOPP cycles this figure is likely to be lower (Federico M *et.al*. 2009). The trial showed no difference in 10 year overall survival (OS) in patients receiving these two regimens (84% v 85%) despite a difference in progression-free survival (PFS) over a shorter follow up of 5 years (68% v 81%). The disconnect between control of lymphoma and overall survival is seen in many contemporary trials. Poorer PFS with less intensive treatment is confounded by fewer secondary malignancies and the ability to salvage recurrent disease in most cases, using high intensity chemotherapy and autologous stem cell transplantation (ASCT). Thus, a European study comparing 8 cycles of ABVD to 4 cycles of eBEACOPP followed by 4 cycles of standard BEACOPP in high risk patients with Stage III/IV disease and an International Prognosis score (IPS) of 3 or more showed no significant difference in disease free survival (DFS) and OS at a median follow up of 3.6 years between the two groups: DFS was 63.7% for ABVD versus 69.3% for BEACOPP ($p = 0.312$); and OS was 86.7% versus 90.3% ($p = 0.208$) (Carde P *et.al*, 2016).

Reduced fertility and severe fatigue are among the most common toxicities in long term survivors from cHL treated with intensive chemotherapy, resulting in relationship and work difficulties that have a negative effect on psyhcological wellbeing (Andrea K *et.al*, 2014). In the GHSG HD15 trial, over one third of women over 30 years experienced severe menopausal symptoms and 89% of men had FSH levels consistent with oligospermia after receiving 6 or 8 cycles of BEACOPP (Behringer K *et.al,* 2013). In contrast to this, ABVD has no appreciable effect upon fertility in women under the age of 35, while in older women the recovery of ovarian function after chemotherapy is delayed in a small proportion of cases (Anderson RA *et.al,* 2018).

The use of Bleomycin in both regimens carries a risk of long term pulmonary toxicity, leading to significant morbidity and mortaility, especially in patients over 40 years or with respiratory co-moribidity. A retrospective analysis by the GHSG over a 10 year period between 1999-2008 found that discontinuation of bleomycin after 4 cycles of BEACOPP did not alter 5 year OS or progression PFS when comparing this group to those patients who received more than 4 cycles of bleomycin (OS difference 1.5% 95%CI -2.6% - 5.5%) (Haverkamp H *et.al,* 2015). However, the complete omission of bleomycin from ABVD in early stage cHL in the GHSG HD13 trial resulted in a lower PFS, leading to the hypothesis that early administration of

bleomycin is important to optimise outcomes, but may be safely omitted in those patients responding well to treatment, forming the basis of a response-adapted approach in the International Response-Adapted Therapy for Advanced Hodgkin Lymphoma (RATHL) trial (Behringer K *et.al*, 2015; Johnson P *et.al*, 2016).

Developing an individualised approach, by intensifying treatment in those patients who stand to gain maximal benefit with high risk disease, while de-escalating treatment in those patients with favourable disease that is likely to be cured by less intensive regimens may reduce the long term toxicity and improve the balance of risk.

Adapting Therapy: by baseline risk or by response to therapy?

The use of the International Prognostic Score (IPS) to stratify patients at diagnosis has historically been used for initial treatment decisions for patients with advanced cHL (Hasenclever D *et.al*, 1998). An updated review with more recent survival outcomes in 2010 showed that although useful for identifying patients with a good prognosis, it is less good at discriminating any subgroup of especially poor outlook who might require more intensive regimens (Moccia A *et.al*, 2012). Attempts have been made to modify its use by the addition of gene expression profiling, but so far without success in prospective trials. The use of a 23 gene expression panel derived from a retrospective analysis, initially thought to give useful prognostic information (Scott DW *et.al*, 2013), was not validated when applied to other studies (Burton CH *et.al*, 2017).

The introduction of 2-(^{18}F)-fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (PET) combined with CT has allowed the metabolic characterisation of involved sites as well as their size and distribution. The use of a semi-quantitative assessment of response (the Deauville 5-point) scoring system has ensured reproducibility of application (Gallamini A *et al,* 2014). A Deauville score of 1-3 after treatment is regarded as negative, 4-5 positive. This scoring system was validated in a large retrospective study which showed a 3 year PFS of 95% in patients who had a negative second PET (PET-2) following 2 cycles of ABVD, compared to 13% in those with PET-2 positive disease, a finding that was independent of the baseline IPS (Biggi A *et.al*, 2013). Thus, early response to treatment appears to be a dominant prognostic indicator in patients with cHL, and has formed the basis of several prospective clinical trials.

The use of interim FDG-PET imaging to guide further treatment decisions based on early disease response was assessed in the complementary International RATHL and French AHL2011 studies. Patients enrolled in RATHL initially received 2 cycles of ABVD before an

interim PET scan. Those who were PET-2 negative (Deauville 1-3) were randomised to receive 4 further cycles of ABVD versus 4 cycles of AVD (omitting bleomycin). Patients with PET-2 positive disease (Deauville 4-5) were escalated to receive either 6 cycles of BEACOPP-14 or 4 cycles of eBEACOPP. After follow up of 3 years, patients who did not receive bleomycin after a negative PET-2 had similar OS and PFS to those receiving a total of 6 cycles of ABVD (3 year PFS and OS 84% and 98% versus 86% and 97% respectively) leading to the conclusion that bleomycin can be safely omitted in patients with early complete metabolic response, while longer term follow up of morbidity and mortality is needed to assess the effect of de-escalation on survival outcomes. Patients with PET-2 positive disease treated with subsequent BEACOPP regimens had a 3 year PFS of 67.5%, which compares favorably with continuation of ABVD in patients following a positive PET-2 of 13-28% in previous trials (Johnson P *et.al*, 2016; Gallamini A *et al,* 2014; Biggi A *et.al*, 2013; Gallamini A *et al,* 2007). The AHL2011 study started with more intense therapy, patients receiving 2 cycles of escBEACOPP and in the experimental arm if PET-2 negative, de-escalated to receive a further 4 cycles of ABVD. This approach was randomised against a non-adapted strategy with patients receiving a total of 6 cycles of escBEACOPP in the standard arm. With a median follow up of 50 months, the 5 year PFS was similar in the standard (86.2%) and the PET driven arms (85.7%; p = 0.68) (Casasnovas O *et.al,* 2018) supporting this strategy as an approach for patients who are at high risk of treatment failure and best served by more intensive regimes. The GHSG HD18 also treated all patients initially with eBEACOPP, and tested de-escalation in patients with a negative PET-2 following 2 cycles of escBEACOPP, randomised to receive either 2 or 6 more cycles of escBEACOPP (the standard was subsequently amended to 4 more cycles following interim analysis). The group receiving a total of 4 cycles of escBEACOPP showed a small statistically significant improvement in 5 year PFS and OS compared with the more extensively-treated group (PFS 92.2% v 90.8% OS 97.7 v 95.4%). Patients with PET-2 positive disease received 6 cycles of escBEACOPP with a 3 year PFS of 92%, although the threshold of PET positivity here included a Deauville score of 3. Post-hoc analysis excluding patients with an interim PET score of 3 showed a 3 year PFS of 87.6% (Borchmann P *et.al*, 2018).

The rate of progression among patients with a negative interim PET who had stage IV disease in the RATHL study was 20%. By comparison, the risk of recurrence among patients with high risk disease initially treated with eBEACOPP in AHL2011 and GHSG18 appears lower: less than 10% in the GHSG18 trial albeit with a stricter definition of interim PET-negative. This suggests that the optimal approach may comprise a combination of risk- and response-adapted approaches; patients with stage IV disease or IPS score over 3 would initially receive 2 cycles of eBEACOPP, with improved disease control and a more reliable negative predictive

value of interim PET than is the case after ABVD. Patients with more favourable baseline characteristics who have a high probability of cure by ABVD could start with this approach and thereby avoid the greater acute toxicity of eBEACOPP. In both cases, de-escalation after a negative interim PET appears justified, either to AVD or to abbreviated eBEACOPP.

Choosing when to give radiotherapy

Radiotherapy has been widely used in the past, originally in extended fields, but more recently for consolidation at sites of bulky disease at presentation or after partial responses to chemotherapy as measured by CT scans, with some retrospective evidence that this led to improved outcomes (Johnson PW *et.al*, 2010). A previous trial demonstrated the absence of benefit from consolidation radiotherapy in patients with a complete response following MOPP-ABV chemotherapy with a median follow up of 79 months (5 year event free survival 84% radiotherapy versus 79% no radiotherapy) (Aleman BM *et.al*, 2003).

Recognition of the risks of long term cardiopulmonary toxicity and secondary malignancies has led to a re-appraisal of this approach. The incidence of lung cancer in cHL survivors who smoke is increased compared to the general population, with survival outcomes worse compared to patients presenting with the same disease with no prior radiotherapy (Milano MT *et.al,* 2011). The risk of coronary heart disease (CHD) when radiotherapy is combined with anthracyclines is well documented, with an excess relative risk of 7.4% per Gray (Gy) resulting in a 2.5 fold increase in CHD risk in patients receiving 20Gy to the mediastinum compared to no radiotherapy (Van Nimwegen FA *et.al,* 2016). Technical advances in planning have allowed more precise targeting of radiotherapy, sparing adjacent tissues but retaining disease control. The GHSG HD15 study investigated the use of PET to guide radiotherapy at the end of treatment in patients with residual masses of <2.5 and found the omission of radiotherapy in patients with a CMR was non inferior (4 year PFS 92%) (Engert A *et.al,* 2012). Therefore a negative interim or end of treatment PET scan is increasingly taken as a signal to omit radiotherapy. Patients enrolled in the RATHL trial were advised to omit radiotherapy following a negative PET scan, which resulted in only 6.5% of patients receiving consolidation radiotherapy, without apparent loss of disease control, even among those who presented with bulky disease (Trotman J *et.al*, 2017). Conversely, patients with a persistently FDG-avid focus at a single site may benefit from radiotherapy to the area, and may thereby avoid the need for more intensive chemotherapy as a result, but there is no prospective data to confirm this as yet. Figure 1 shows a theoretical combined risk and response adapted approach incorporating both current standard and experimental approaches for frontline therapy in younger patients.

Adding a new agent to initial therapy

Brentuximab vedotin (BV) is an antibody-drug conjugate consisting of an anti-CD30 monoclonal antibody combined with an anti-microtubule agent which is internalised and cleaved, disrupting the cell cycle and leading to apoptosis in the target cell. Initial attempts to add BV to ABVD resulted in severe pulmonary toxicity owing to the interaction with bleomycin (Younes A *et.al,* 2013), but a subsequent series of patients treated with BV+AVD showed good tolerability and promising response rates (Connors JM *et.al*, 2017). The phase III ECHELON-1 trial randomised patients with Stage III-IV cHL to receive 6 cycles of ABVD or BV+AVD. Interim PET scans were performed, but changes in therapy were only permitted for those with a score of 5. The primary survival outcome measure was PFS, modified to include as an event those patients with a Deauville score of 3 at the end of treatment who subsequently went on to receive further anticancer therapy. This was an unblinded study and therefore potentially prone to bias in this respect. With a median follow up of 2 years there was a 4.9% difference in modified PFS in favour of the AVD-BV group with no difference in 2 year EFS or OS (Connors JM *et.al*, 2018). A higher incidence of grade 3-4 peripheral neuropathy and febrile neutropenia was reported in the BV+AVD group but the myelosuppression could be mitigated by the use of prophylactic G-CSF. The results suggest a modest improvement in disease control at the expense of greater toxicity and substantial drug costs, but this approach may be attractive for patients who cannot receive bleomycin due to age or co-morbidity. Further studies are underway to incorporate BV into a BEACOPP-like regimen, which may prove valuable for those with high risk disease at presentation (Eichenauer D *et.al*, 2017).

Refining the models and testing new therapies:

Improving the baseline prognostic information remains a useful goal. The initial FDG-PET may provide some help, through calculation of metabolic tumour volume (MTV) and total lesion glycolysis (TLG), both of which may be useful to help stratify patients by risk group. Observations from the RATHL trial found that patients with a high TLG at baseline were more likely to suffer treatment failure compared to those with low uptake (standardised uptake of ≤2.5 TLG to calculate volume of disease). In patients with a negative PET2 the 3 year rate of progression or death from HL with high and low TLG was 21.9% versus 10.9% respectively which also remained true at 5 years (31.1% versus 13.1%) This retained significance when adjusted for other variables including age and B symptoms, and may provide a better means of predicting treatment failure than IPS, although prospective validation of this is clearly needed (Pike LC *et.al,* 2017).

Patients with an interim PET score of 5, although few in number, appear to require a different approach: escalation from ABVD to eBEACOPP in the RATHL study failed in 20 of 37 cases. The Italian HD0801 study of patients escalated to high dose ifosfomide-based salvage chemotherapy with ASCT or allogenic stem cell transplant following a Deauville score of 3 and above on interim imaging showed that the 2 year PFS of this group was close to that of patients with PET scores 1-2 (75% versus 81% respectively), although it should be noted that patients with an interim score of 3 are likely to have good outcomes without dose escalation (Zinzani PL *et.al*, 2016).

Newer agents such as immune checkpoint inhibitors may prove useful in the group with relatively chemorefractory disease, given the excellent response rates seen in heavily pre-treated patients following ASCT (Ansell SM *et.al,* 2015; Chen R *et.al*, 2017). Nivolumab and pembrolizumab are anti-programmed cell death IgG4 monoclonal antibodies (anti PD-1) that are both approved for treatment of cHL within the relapsed setting. Both inhibit the PD-1 receptor interaction on tumour cells with its ligands on activated T Cells, downregulating T Cell responses within the tumour microenvironment. Molecular studies have shown that patients with cHL frequently have alterations of chromosome 9p24.1, a locus containing the ligands PD-L1 and PD-L2. These give rise to copy-number alterations and rearrangements, and associated PD-L1 and/or PD-L2 overexpression, potentially facilitating immune evasion and modulating signaling between the T-cells and the malignant B-cells. Such alterations are correlated with advanced stage and reduced PFS (Roemer MG *et.al*, 2016). A phase II trial investigating nivolumab treatment in patients with recurrent disease after high dose therapy and BV had an impressive overall response rate (ORR) of 66%, with a median duration of response of 8.7 months, leading to its approval as 4th line treatment in relapsed cHL post-stem cell transplant (Younes A *et.al,* 2016). Extended follow up of this cohort saw the median duration of response extended to 16.6 months (95% CI, 13.2 to 20.3 months), with a median PFS of 14.7 months (95% CI, 11.3 to 18.5 months) (Armand P *et.al* 2018). Although most responses have not proven durable in this population of patients, there is a theoretical attraction to using a non-cytotoxic approach in patients with chemorefractory disease during initial therapy. The use of Nivolumab sequentially combined with AVD chemotherapy in the frontline setting was evaluated in a recent Phase II trial. Four cycles of Nivolumab monotherapy were given at 2 week intervals, followed by 6 cycles of AVD plus Nivolumab. The tolerability of this regime was favorable, with no grade 5 toxicity and no pneumonitis reported. The ORR was 43 of 51 patients (84%) with a median follow up of 11 months and a complete response rate (CRR) rate of 67% (Ramchandren R *et.al*, 2018). Future studies should test the use of anti-PD1 antibodies in patients with a poor response to initial therapy as assessed by positive interim PET scans.

Initial Treatment in Older Patients

Conventional chemotherapy Regimes

Patients over the age of 50 with advanced HL show inferior outcomes compared to younger groups, and in the older population the gains in survival seen over the last 30 years have not been replicated (Boll B *et.al,* 2013). There is a paucity of trial data to guide treatment decisions within the elderly population, an increased incidence of toxicity and higher treatment failure rates when compared to younger patients. There is no recognised standard frontline treatment and it is often difficult to give bleomycin and anthracycline-containing regimes due to the increased risk of cardiopulmonary toxicity. The GHSG HD9 elderly trial randomized patients between COPP/ABVD or BEACOPP baseline, but found toxicity to be substantial with the more intensive regimen, with 21% treatment-related deaths after BEACOPP compared with 8% after COPP/ABVD (Ballova V et.al, 2005). Five-year survival was only 50% for both arms.

A large non-randomised study in patients over 60 years with advanced cHL (the SHIELD study), was one of the first to incorporate a co-morbidity scale to assess fitness for a multi-agent chemotherapy regime (SNLG modified ACE-27 co-morbidity scale). If patients were designated too 'frail' to receive the alternating regimen VEPEMB, they were given another treatment at their physician's discretion including ABVD, ChlVPP or radiotherapy (this arm was also open to 'non-frail' patients). For the 72 patients fit enough to receive VEPEMB, 3-year OS and PFS were 66% and 58%, respectively. Interestingly, independent of chemotherapy regime, no patients who were 'frail' achieved a CR at the end of treatment (Proctor SJ *et.al,* 2012). A small randomised trial compared VEPEMB to ABVD in carefully-selected non-frail patients aged 65-80, and found the results with ABVD to be slightly better, with 5-year PFS rates 48% vs 70% and OS 63% vs 77%, although these differences were not significant owing to the small size of the study (Zallio F *et.al,* 2016). Similar results were seen in the RATHL trial, where the 5 year PFS among 43 patients over 65 years was 65%, with a 5 year OS of 83%. This group is also a selected cohort, with 93% de-escalated to 4 cycles of AVD while 7% escalated to BEACOPP after a positive interim PET. The most common causes of death in this age group were cardiac (5%) and secondary malignancy (7%) compared to death related to cHL and further salvage regimes in the younger patient cohort. Figure 2 shows the cause of death by age group in this trial after 5 years of follow up.

The use of ChlVPP chemotherapy has a favourable toxicity profile, with a reported 10 year OS of 40% across a broad age range, and it is therefore commonly used in less fit elderly patients (Selby P *et.al,* 1990). Patients over 60 years treated with ChlVPP in the SHIELD study had an ORR of only 7 of 19 patients (36%) and long-term survival in the elderly population is

likely to be substantially lower than 40%. However, this regime has moderate benefit and may improve the quality of life of elderly patients with other co-morbidities in whom more intensive chemotherapy regimens are contraindicated.

The ChlVIPP/EVA hybrid regime (Chlorambucil, Vinblastine, Procarbazine, Prednisolone, Etoposide, Vincristine and Doxorubicin) has demonstrated efficacy in fit elderly patients with no cardiac co-morbidity, but other toxicities include mucositis, peripheral neuropathy and neutropenic sepsis, resulting in a high rate of hospital admissions. In a randomised trial in patients with any stage cHL up to 75 years, 6 cycles of CHlVIPP/EVA gave a 5 year PFS of 82%, although 58% of these patients also received radiotherapy to sites of bulky disease or residual abnormalities at the end of treatment (Radford JA *et.al,* 2002). Comparison to ABVD in a large randomised trial showed equivalent results with the hybrid regimen (Johnson PWM *et.al*, 2005), but it does offer the option of proven treatment that avoids bleomycin in this group, with the possibility to de-escalate to AVD if an interim PET scan is negative.

Brentuximab vedotin combinations

Brentuximab vedotin monotherapy has shown limited efficacy in the BREVITY Phase II trial, which recruited patients over 60 years with an ECOG score of 3 or less who were considered ineligible for conventional therapy (Gibb A *et.al,* 2017). 63% of patients had Stage III-IV disease and received 4 cycles of BV, with a complete metabolic response (CMR) rate in this cohort of 26%, and ORR 84%. These responses were unfortunately short, with a median PFS of 7.4 months and a high toxicity rate in this population with multiple co-morbidities and a median age of 76. Grade 3-4 toxicity was seen in 77% of patients including peripheral neuropathy, myelosupression and infection, leading to treatment discontinuation and a high proportion of dose reductions. However, a subgroup analysis of patients receiving AVD+BV ≥60 years in the ECHELON-1 trial showed that this was equally effective when compared to ABVD (HR 1.01 95%CI 0.59-1.73) sparing this population from the pulmonary toxicity associated with bleomycin (Connors JM *et.al*, 2018).

Sequential therapy with frontline BV and AVD was investigated by Evens.et.al in a Phase II study (Evens AM *et.al,* 2018); patients received 2 cycles of BV followed by 6 cycles of AVD. Those with disease response received a further 4 cycles of BV as consolidation therapy. 48 patients were recruited with a median age of 69 and ECOG of 1. The 2 year PFS within the intention to treat population was 84% with an impressive 2 year OS of 93%, making this an attractive option for fit older patients able to tolerate anthracycline containing chemotherapy. This regimen averts the risk of pulmonary toxicity associated with bleomycin, whilst offering

response rates comparable to the more intensive CHIVPP/EVA hybrid regime and without additional consolidation radiotherapy.

Brentuximab vedotin combined with bendamustine or dacarbazine was evaluated as an alternative approach in patients over 60 who were unable to receive conventional chemotherapy. In this group, with a high incidence of three or more co-morbidities and a median age of 76 years, the incidence of serious adverse events associated with bendamustine was high (67%) and enrolment into this study arm was stopped. However, BV combined with dacarbazine was less toxic, with an ORR of 100% and a CR rate of 62% in 22 patients with a median age of 69 years (Yasenchak C *et.al,* 2015). This highlights the complexities associated with choice of treatment in elderly patients and the need for further studies incorporating tools that assess frailty and quality of life to improve survival and toxicity outcomes for this diverse expanding population.

Incorporation of Comprehensive Geriatric Assessment (CGA)

Holistic assessment of elderly patients with complex medical, social and psychological needs within the field of geriatrics has been revolutionised using CGA, resulting in improved survival outcomes, reduced hospital stay and improvement in quality of life. The use of CGA in Oncology is challenging due to the time constraints, therefore identifying patients that would benefit from this approach requires a validated screening tool. The G8 questionnaire was developed by Bellera et.al. specifically within the field of Oncology and includes 8 areas for assessment including nutritional status, self-perception of health and number of medications (see Figure 3) (Bellera CA *et.al*, 2012). A cut-off score of 14 provided a good sensitivity estimate (85%) with a specificity of 64%. A third of patients with cHL are >60 years and treatment decisions guided primarily by physician experience (CRUK, 2017). The use of the G8 questionnaire in these patients may prove useful in identifying those who would benefit from specialist geriatric support.

Conclusions

A mix of risk- and response-adapted approaches to enable the de-escalation of treatment in patients with low risk disease and intensification in those with high risk or chemoresistant disease is an attractive option for first line therapy, to optimise cure rates and reduce the long term mortality and morbidity associated with intensive treatment. An initial approach could start with ABVD for low risk and eBEACOPP for high risk patients, with de-escalation after interim PET to AVD in patients with scores of 1-3 and intensification to eBEACOPP or

autograft in those with scores of 4-5, according to risk group at diagnosis. Radiotherapy has a potential role in isolated chemoresistant disease but is becoming less widely used in the context of a negative PET, therefore reducing the long term toxicities associated with its use in younger patients. Newer agents may offer choices for poor prognosis groups, for example anti-PD1 after a positive PET2, and possibly BV for advanced stage or those unable to have bleomycin. Older patients need screening for CGA and stratified treatment according to the different competing risks and comorbidity, with possible options including ABVD, ChlVPP/EVA or sequential BV+AVD.

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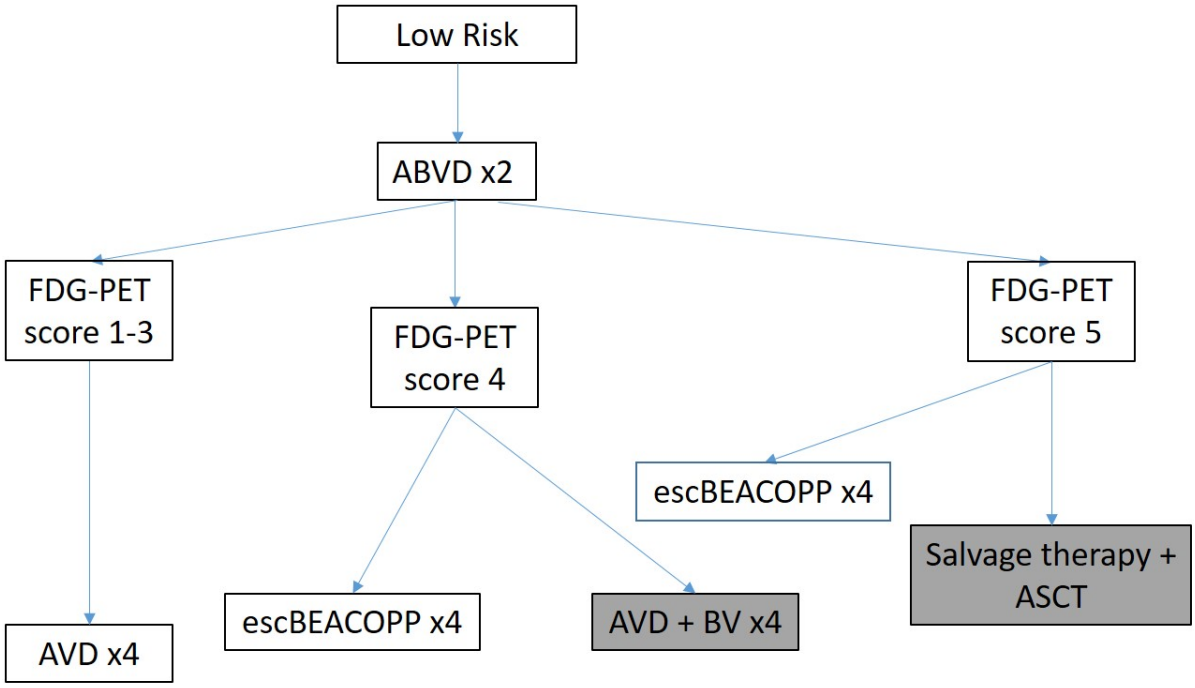
Table 1: Recent clinical trials of initial therapy in patients <60 years

Trial	Regime	N	Stage III/IV (%)	High risk (%) IPS ≥4	PFS (%)	OS (%)	Secondary Malignancy (%)
RATHL	ABVD #2 PET negative AVD #4	470	59	16	86 (3yr)	97 (3yr)	2.8
	ABVD #2 PET negative ABVD #4	465	58	14	84 (3yr)	98 (3yr)	2.4
	ABVD #2 PET positive escBEACOPP #4 or BEACOPP-14 #6	172	58	30	66 (3yr)	88 (3yr)	1.7
AHL Lysa 2011	escBEACOPP #2 PET negative ABVD #4	346	88*	58**	92 (4yr)	NA	NA
	escBEACOPP #2 PET positive escBEACOPP #4	51			72 (4yr)	NA	NA
	escBEACOPP #6 (non-PET driven)	413			87 (4yr)	NA	NA
GHSG HD18	escBEACOPP #2 PET positive escBEACOPP #4-6	219	78	13	91 (3yr)	97 (3yr)	3
	escBEACOPP #2 PET positive escBEACOPP plus R #4-6	220	75	22	93 (3yr)	94 (3yr)	1
GHSG HD15	escBEACOPP #6	705	83	15	86 (5yr)	92 (5yr)	4.7
	escBEACOPP #8	711	85	15	90 (5yr)	95 (5yr)	2.4
	BEACOPP-14 #8	710	85	17	85 (5yr)	95 (5yr)	3.1
US intergroup SWOG trial	ABVD #2 PET negative ABVD #4	370	100*	51*	82 (2yr)	NA	1
	ABVD #2 PET positive escBEACOPP #6	55			64 (2yr)	NA	6.1
Viviani et.al	ABVD #6-8 if <CR or PD then ASCT	168	NA	53*	73 (7yr)	84 (7yr)	1
	escBEACOPP #4 + BEACOPP #4 if <CR or PD then ASCT	163	NA		85 (7yr)	89 (7yr)	1
EORTC 2012	ABVD #8	275	100	100**	73 (4yr)	87 (4yr)	3
	escBEACOPP #4 + BEACOPP-#4	274	100	100**	83 (4yr)	90 (4yr)	4
GHSG HD12	escBEACOPP #8 + RT	392	83	15	89 (5yr)	92	3.6
	escBEACOPP #8	395	84	18	87 (5yr)	91	2.3
	escBEACOPP #4 + BEACOPP #4 + RT	393	83	19	87 (5yr)	91	2.5
	escBEACOPP #4 + BEACOPP #4	394	85	15	84 (5yr)	90	0.8

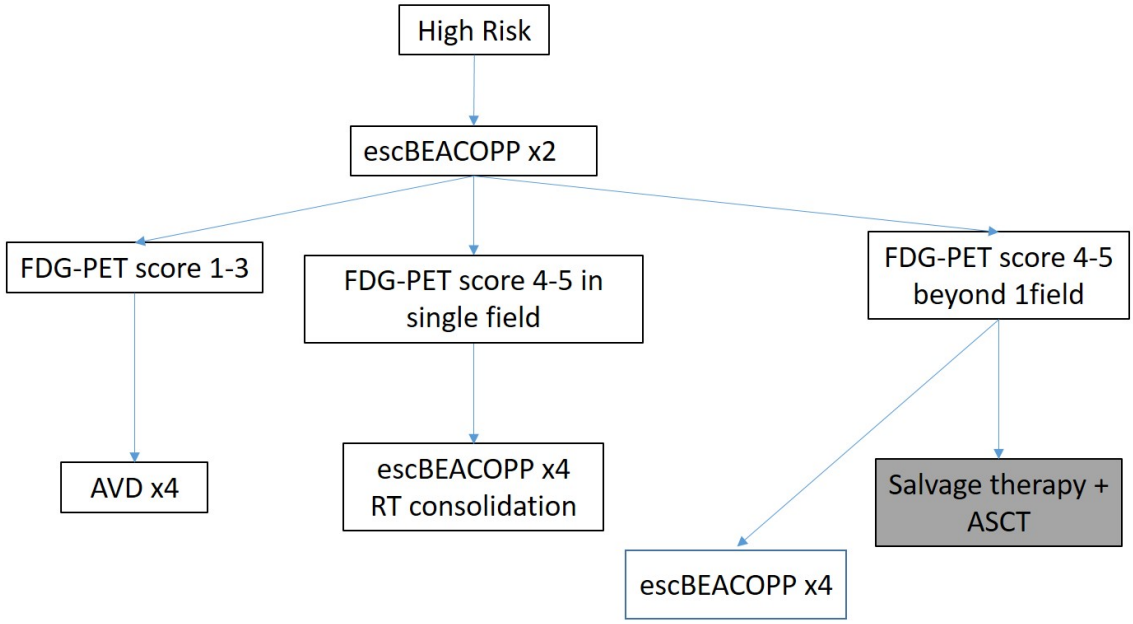
* Stage of whole trial cohort

** IPS score ≤3

Figure 1 – Combined risk and response adapted treatment algorithms for younger patients (approaches considered experimental in shaded boxes)



High risk at presentation:



*Definition of high risk may be IPS score 3-7 or 4-7, or stage IV disease.

Figure 2 – Cause of death by age group in the RATHL trial

Cause of death	18-35 N=674	36-50 N=295	51-65 N=190	65+ N=43	All N=1202
Hodgkin Lymphoma	9 (1.3)	4 (1.4)	13 (6.8)	1 (2.3)	27 (2.3)
Cardiac	1 (0.2)	1 (0.3)	1 (0.5)	2 (4.7)	5 (0.4)
Other (unrelated to treatment or HL)	2 (0.3)	2 (0.7)	2 (1.1)	0	6(0.5)
Second malignancy	1 (0.2)	1 (0.3)	6(3.2)	3 (7.0)	11 (0.9)
TRM – salvage	3 (0.5)	4 (1.4)	4 (2.1)	0	11 (0.9)
TRM – first line	0	3 (1.0)	4 (2.1)	1 (2.3)	8 (0.7)

Percentages in brackets are of the total number treated

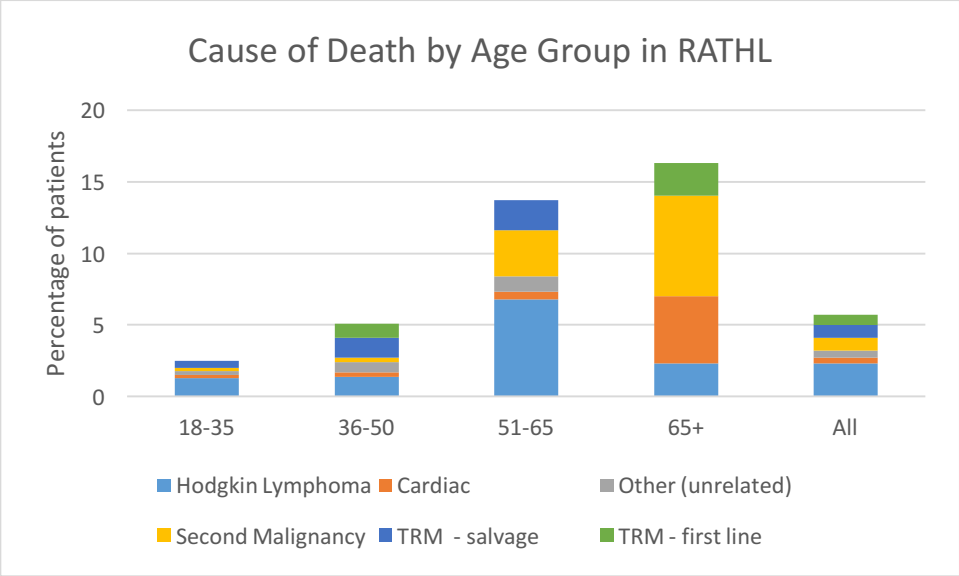


Figure 3 – G8 Questionnaire

A Has food intake declined over the past 3 months due to loss of appetite, digestive problems, chewing or swallowing difficulties?

0: severe decrease in food intake

1: moderate decrease in food intake

2: no decrease in food intake

B Weight loss during the last 3 months?

0: weight loss >3 months

1: unknown

2: weight loss 1-3 kg

3: no weight loss

C: Mobility

0: bed or chair bound

1: able to get out of bed/chair but does not go out

2: goes out

D: Neuropsychological problems

0: severe dementia or depression

1: mild dementia or depression

2: no psychological problems

E: Body mass Index (BMI)

0: <19

1: 19 to <21

2: 21 to <23

3: 23 and >23

F: Takes more than 3 medications per day

0: yes 1: no

G: In comparison with other people of the same ago how does the patient consider his/her health status?

0: not as good

1: as good

2: better

H: Age 0: >85

1: 80-85

2: <80 **Total Score 0-17**