How to treat classical Hodgkin's lymphoma in older patients: Belgian expert opinion

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On behalf of the lymphoproliferative disease committee BHS

SUMMARY

Classical Hodgkin's lymphoma (cHL) is a rather rare disease with an incidence of 2-3/100,000 per year and typically presents in patients at the age of 20-30. It is however well known that a second peak occurs at the age of 60-65 years.[1] Nowadays Hodgkin is a curable disease for most of the younger patients but treatment is more difficult and less successful in the older patient population. In this review, we want to summarise the possibilities for the treatment of cHL patients above 60 years, with a focus on evidence from the rather rarely available clinical trials. We also look at future treatments. In this article we will use the term 'older patients' for patients of 60 years and older at diagnosis. We will make a distinction between fit patients older than 60 years and frail or vulnerable patients (so called elderly).

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BACKGROUND

There is a bimodal age distribution in Hodgkin lymphoma with two incidence peaks, one in young adulthood and one around 60-70 years. However, with the aging of the population we see an increased incidence of cHL in the older patients. In this article we will use the term 'older patients' for patients of 60 years and older at diagnosis. We will make a distinction between older than 60 years fit and frail patients. In 2018, 311 new cases of cHL were registered by the Belgian Cancer Registry, 170 male patients and 141 women. Of those 82 (26%) were older than 60 years (*Figure 1*).

Treatment of Hodgkin's lymphoma has changed rapidly in the last decade and the disease has become curable for most of the younger patients. It is well described that the disease behaves differently in older patients. Besides the comorbidities and polypharmacy that have to be taken into account, patients often present with more aggressive disease with B symptoms and advanced stage at diagnosis. The mixed cellularity subtype is seen more often, as is EBV positivity. cHL in older patients might be a biologically more aggressive disease. Presence of a large mediastinal mass is less common.[2]

When treating patients above 60 years we encounter more comorbidity, more toxicity of standard treatments and unfortunately also a higher mortality rate. Moreover, those patients are underrepresented in clinical trials: in most studies, only 5-10% of patients are aged above 60. In clinical trials from the German Hodgkin's Study Group (GHSG), the 5-year progression-free survival (PS) and overall survival

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FIGURE 1. Hodgkin lymphoma: number of new diagnoses and age standardised by sex and subtype, Belgium 2018.[1]

	Males						Females					
	N			WSR			N			WSR		
Belgium 2018	Total	<60y	60+	Total	<60y	60+	Total	<60y	60+	Total	<60y	60+
Hodgkin lymphoma	202	149	53	3,4	3,3	4,1	162	111	51	2,6	2,4	3,7
Hodgkin lymphoma, nodular lymphocyte predominant	14	13	1	0,3	0,3	0,1	8	4	4	0,1	0,1	0,4
Classical Hodgkin lymphoma	170	126	44	2,8	2,8	3,4	141	103	38	2,3	2,3	2,8
Hodgkin lymphoma, NOS & varia	18	10	8	0,2	0,2	0,6	13	4	9	0,1	0,1	0,5

WSR: age standardised incidence using the World standard population (n/100,000 person years).

(OS) were significantly lower in older patients: 60 and 65% respectively *versus* 80 and 90% in younger patients, for studies conducted between 1988 and 1998.[2] In addition, other (patient reported) endpoints such as quality of life and physical functioning are also highly relevant, but unfortunately hardly assessed in studies.

Because this is an important challenge in daily practice, we here summarise the available evidence on how to treat cHL in patients above 60 years in the Belgian reimbursement setting in 2021.

GERIATRIC ASSESSMENT

Older patients are a heterogeneous population with large differences in comorbidity, functional capacity and psychological and physical reserves.[3]

Patients can be crudely assessed by performance status and the Charlson's comorbidity index or CCI, the latter predicting the 10-year survival in patients with comorbidities. In daily practice, the 'eye' or judgement of the treating clinician is often used to assess frailty and eligibility for standard chemotherapy. A recent study by Van Walree *et al.* showed a very poor correlation between the clinical judgment and geriatric assessment and even a low correlation between the assessments of an oncologist and a general practitioner.[4]

Different specialised multidisciplinary geriatric assessment modalities focusing on somatic (age, polypharmacy, nutritional status, comorbidities, cognition, physical capacity, etc.), psychological (mood), functional (ADL/IADL) and social (social support) domains, exist to help the clinician to identify frail patients. Geriatric assessment, even in patients with a good performance score, can detect impairments in different geriatric domains, which may be predictive of higher treatment-related toxicity, treatment delays and non-completion, hospitalisation and mortality. Frailty screening tools were also developed to identify older patients who require a comprehensive geriatric assessment.[3] Scheepers *et al.*, very recently updated their systemic review on geriatric assessment in haematological malignancies in general, details can be consulted in their study. Specific data on Hodgkin lymphoma are scarce.

Moreover, it can be challenging to distinguish between disease-related and patient-related impairment. A multidisciplinary approach, with consultation of a geriatrician might be useful in the less obvious cases.

The SHIELD program (results discussed later in the article) included patients with Hodgkin lymphoma of 60 years of age or older and prospectively evaluated clinical features and outcome in a large patient cohort (n = 175). The outcome of patients designated frail by comorbidity score and unsuitable for aggressive chemotherapy remains a major concern.[5]

We therefore discuss in this manuscript treatment for patients above 60 years but eligible for intensive treatment (without precluding comorbidities and low scoring in comprehensive geriatric assessment), for which the goal of treatment is still cure, separately from older frail patients that are unsuitable for *e.g.* ABVD and for whom the goal is palliation.

STANDARD OF CARE FIRST LINE TREATMENT IN OLDER FIT PATIENTS

EARLY STAGE DISEASE

According to our Belgian Guidelines, the standard care for patients with early favourable disease is combined modality treatment with two or three courses ABVD followed by

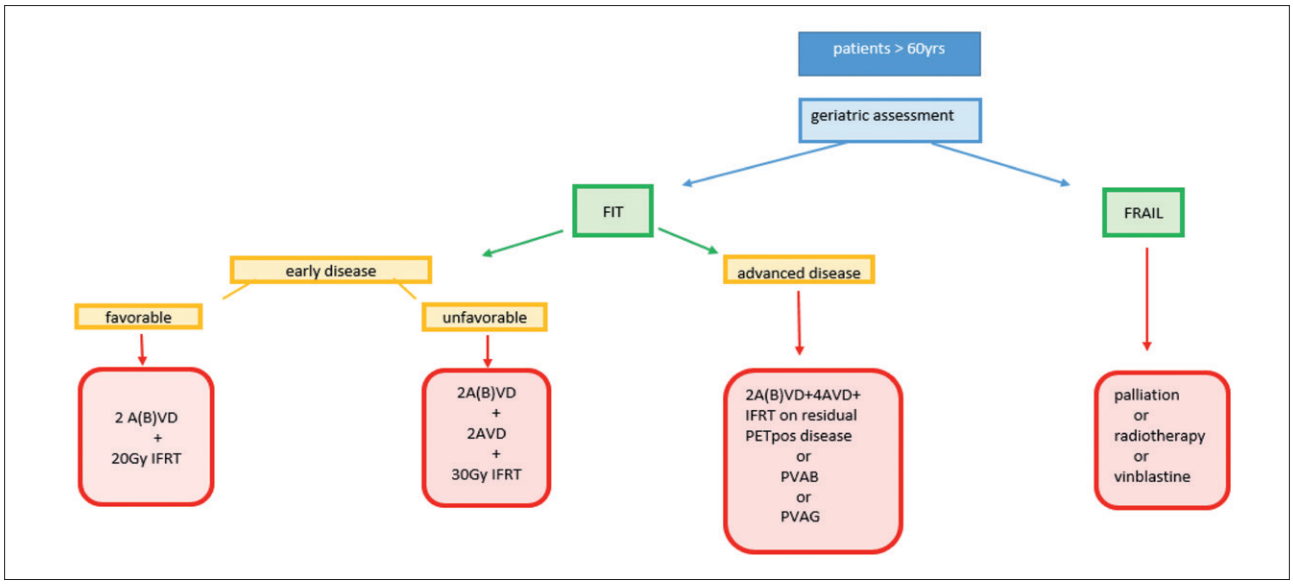

FIGURE 2. First-line treatment for HD in older patients.

20 Gy involved field radiotherapy (IFRT).[6] Patients with early unfavourable disease receive four courses of ABVD followed by 30 Gy IFRT. Treatment is adapted according to the results of the interim PET-CT after the second course of ABVD. Patients with PET positive disease after two cycles of ABVD receive treatment intensification with BEACOPP esc chemotherapy.

ABVD is generally feasible in older patients without cardio-pulmonary comorbidities. However, upgrading chemo-therapy toward BEACOPP escalated (BEACOPPesc) is not due to excessive toxicity.[7]

Sub analysis of the patients within the HD10 and HD11 trials showed that only 68/528 patients were above 60 years in the favourable group and 49/654 in the unfavourable group.[8] For older patients treatment delay, incidence of grade 3-4 adverse events and treatment related mortality were higher. In this sub-analysis, the 5-year PFS in patients > 60 years was 79% *versus* 90% in younger patients, being irrespective of the number of cycles administered.

Especially bleomycin toxicity is higher in older patients, with a high incidence of severe, lethal bleomycin induced pulmonary toxicity. Toxicity of bleomycin is particularly higher in patients receiving more than two cycles of ABVD.[9] Therefore, we advise to omit bleomycin after the first two cycles in older patients.

Based on expert opinions of Belgian haematologists and pneumologists, although evidence from clinical trials is lacking, we advise that in case of pre-existing reduced pulmonary function (DLCO <60%) before treatment, the use of bleomycin should be avoided as from cycle 1.

The role of radiotherapy has also been investigated. In the GHSG HD8 trial there was a higher radiotherapy-associated toxicity in patients older than 60 years compared to those younger than 60 with a difference of 26.5% *versus* 14.4%. This difference is even higher in patients receiving extended field radiotherapy.[10]

In the past, alternative schedules such as CHOP 21, have also been investigated for treatment of cHL in the older patients.[11] In a retrospective, single centre study 29 patients, with a median age of 71 years, were treated with 2-4 cycles of CHOP followed by IFRT in case of stage I-II disease and 6-8 cycles CHOP for advanced disease. With a short follow-up, the 3-year PFS and OS were 79 and 76%, respectively. Unfortunately, no longer follow up results are available for this cohort. Results of randomised trials comparing ABVD and CHOP, are not available for this group.

Other alternative treatment schedules studied for both early unfavourable and advanced disease are VEPEMB (vinblastine, cyclophosphamide, prednisolone, procarbazine, etoposide, mitoxantrone, and bleomycin), PVAG (prednisone, vinblastine, doxorubicin and gemcitabine) and PVAB (prednisone, vinblastine, doxorubicine and bendamustine).[12-14] Those schedules will be discussed in the section on advanced disease. Due to short follow-up and low patient numbers, it is difficult to draw conclusions for patients with early stage disease. There are ongoing trials by the GHSG. For patients presenting with progressive or stable disease at interim PET CT scan, we would consider to change the treatment to an alternative schedule, as discussed further in this article in the section on refractory disease. As mentioned previously, upgrading chemotherapy to BEACOPP esc is not feasible in this population.

TABLE 1. First line treatment for older patients fit for therapy.

reference	Regimen	N (patients) > 65	stage	efficacy	safety
Böll B et al. (8): subanalysis of HD10 and HD11	ABVD 2 or 4 cycles + IFRT	68 favourable 49 unfavourable	Early stage favourable Early stage unfavourable	5yr PFS: 79%	Higher incidence of gr 3-4 AEs
Kolstad et al. (11) retrospective, single centre	CHOP21 2-4 cycles + IFRT CHOP21 6-8 cycles	29 in total	Early stage Advanced stage	3yr PFS: 79% 3yr OS: 76%	Well tolerated
Johnson P et al (16)	ABVD 6 cycles (PET adapted treatment)	N> 60: 115 (of 1,412 in total) ABVD 38 AVD 44 Beacopp 18	Advanced stage	3yr PFS: 82.6% 3yr OS: 95.8% No separate analysis for > 60yr !	Well tolerated.
Proctor S et al. (5) SHIELD trial	VEPEMB 6 cycles	72 advanced stage (2B-4)	Advanced stage (2B-4)	3yr PFS: 58% 3yr OS: 66%	Treatment related mortality 7%
Zallio et al. (12) Randomised trial comparing VEMBEP vs ABVD	VEPEMB 6 cycles vs ABVD 6 cycles +/- IFRT on residual or bulky disease	37 in total	Advanced stage	5yr PFS/OS: 48%/63% vs 5yr PFS/OS: 70%/77%	Overall treatment related mortality 4%
Böll B. et al. (13) multicentre phase II trial	PVAG 6 to 8 cycles +/- IFRT	59 (95% advanced stage)	Advanced stage	3yr PFS: 58% 3yr OS: 66%	Well tolerated, TRM 2%
Ghesquieres H. et al. (14) multicentre phase II trial	PVAB 6 cycles	89	Advanced stage (2B with risk factors, 3, 4)	2yr PFS: 61% 2yr OS: 84%	4 deaths due to treatment related events. Frequent infections
Böll B et al. (19) phase 2 trial	Brentuximab vedotin + CAP	49	Advanced stage	1yr PFS: 79%	Low toxicity, feasible
Evens A et al. (20) subanalysis of the phase 3 ECHELON-1 trial	ABVD 6 cycles vs Brentuximab vedotin + AVD 6 cycles	186 in total	Advanced stage	2yr modified PFS: 71% vs 2yr modified PFS: 70%	Higher toxicity rate More febrile neutropenia: G-CSF warranted for A+ AVD
Evens et al. (21) multicentre phase 2 trial	Brentuximab vedotin 2 cycles followed by 4 cycles of AVD + IF CR or PR: 4 cycles of BV	48	81% stage III and IV	2yr PFS: 84% 2yr OS: 93%	Grade 3 or 4 neutropenia in almost half of patients Febrile neutropenia in 8%
Cheson B et al. (24) multicentre phase 2 ACCRU trial	Brentuximab vedotin + nivolumab 8 cycles	46 (older or unfit for chemo younger pts)	All stages except IA	48% complete metabolic response Trial did not meet predefined criteria: stop	48% peripheral neuropathy (11% grade 3)
Yasenchak C et al. (25) phase 2 trial	Brentuximab vedotin + nivolumab up to 16 cycles	21	Majority advanced stage	72% CR, 28% PR, no long follow-up data	Peripheral neuropathy is most common adverse event

TABLE 2. Risk criteria in early stage Hodgkin's lymphoma according to EORTC/LYSA and GSHG.

EORTC/LYSA classification	GSHG classification
bulky mediastinal mass	bulky mediastinal disease
age ≥ 50 years	extranodal site
ESR ≥ 50 without B symptoms	ESR ≥ 50
ESR ≥ 30 with B symptoms	≥ 3 nodal sites
≥ 4 nodal areas involved	
Presence of one or more of these risk factors indicates unfavourable disease.	

CONCLUSION

We advise for older fit patients with favourable disease to be treated with two cycles of ABVD, followed by 20 Gy IFRT. For older patients with unfavourable disease we recommend two cycles of ABVD followed by two cycles of AVD (omission of bleomycin) followed by 30 Gy IFRT (*Figure 2, Table 1*).

Note: Looking at the risk classification following EORTC criteria, age itself is a risk factor and therefore we should classify every patient above 60 as having early unfavourable disease. However according to the GHSG criteria age, is less important and in their trials they make the difference, even in older patients, between favourable and unfavourable early stage disease. Considering the fact that the GHSG is the group with the most published trials on this topic, we decided to keep this classification in this article (*Table 2*).

ADVANCED STAGE DISEASE:

In younger patients with advanced disease, treatment is started with either ABVD or BEACOPPesc in a PET-CT adapted strategy. In PET-negative patients, treatment is continued by four cycles of ABVD after BEACOPP esc or four cycles of AVD in patients initially treated with ABVD. In PET-positive patients, treatment is respectively escalated to or continued by four cycles of BEACOPPesc.

As mentioned earlier, treatment with BEACOPPesc is not feasible in older patients.[7]

On the other hand, ABVD is also more toxic and less effective in older patients.[8] This was also confirmed by amongst others the United Kingdom SHIELD study where treatment related mortality was up to 10%.[5] Toxicity leads to dose reductions and treatment delay and it has been shown by Landgren *et al.*, that a relative dose intensity (RDI) above 65% is associated with a better OS in older cHL patients -those numbers are certainly not always reached for a treatment regimen of six cycles ABVD.[15]

For patients negative at PET2 (interim PET after two cycles ABVD), omission of bleomycin from the ABVD regimen resulted in a lower incidence of pulmonary toxic effects than with continued ABVD but not significantly lower efficacy in the multicentric phase III RATHL trial.[16] For PET2 negative older patients is four additional cycles of AVD thus a reasonable option.

As mentioned for early stage disease, we advise that in case of pre-existing reduced pulmonary function (DLCO <60%) before treatment, the use of bleomycin should be avoided as from cycle 1.

Several clinical trials have investigated other possible schedules such as ChlVPP (chlorambucil, vinblastine, procarbazine and prednisolone), ODBEP (vincristine, doxorubicin, bleomycin, etoposide, and prednisone), VEMBEP, *etc.* However, most attempts have failed due to unsatisfactory efficacy or due to unacceptable toxicity.

The SHIELD program was an initiative of several Hodgkin lymphoma working groups acknowledging the fact that ABVD was too toxic, however no agreement upon a valuable alternative treatment schedule was obtained.[5] Of 175 studied patients, 103 were included in the phase II VEMBEP (vinblastine, cyclophosphamide, prednisolone, procarbazine, etoposide, mitoxantrone, and bleomycin) trial after being assessed as non-frail according to comorbidity scales, ADL and IADL screening. Median age of the patients treated with VEMBEP was 73 years (range, 61-85 years). A total of 72 patients with advanced-stage disease (stage 2B, 3 or 4) received six cycles of VEMBEP. CR rate was 61%

with 3-year OS and PFS of 66 and 58%, respectively.

In the more recent published randomised trial comparing reduced intensity VEMBEP *versus* ABVD, 37 patients in total with advanced disease were treated with either six courses ABVD or six courses VEMBEP, followed by IFRT to residual disease or former bulky disease in both groups.[12] Five-year PFS rates were 48% *vs.* 70% [*P* = 0·068] and 5-year overall survival (OS) rates were 63% *vs.* 77% (P = 0·254) for VEPEMB compared to ABVD. Overall treatment-related mortality was 4%.

An alternative treatment strategy might be PVAG (prednisone, vinblastine, doxorubicin and gemcitabine).[13] In a multicentre phase II study including 59 patients (95% having advanced disease) treatment consisted of six to eight cycles of PVAG and additional radiotherapy. Median age of the included patients was 68 years. CR was reached in 78% with a 3-year OS and PFS of 66 and 58%, respectively. The schedule was well tolerated and treatment related mortality (TRM) was low (2%).

More recently, the French LYSARC presented the preliminary results of a trial with six cycles of PVAB (prednisone, vinblastine, doxorubicine and bendamustine).[14] In the 89 patients, median age 68 years, a CMR (complete metabolic response) rate of 77.5% was reached. The 2-year PFS was 61.3% and within the group of patients who attained a CMR the 2-year PFS was 73.3%. Longer follow up is needed but the 2-year OS was 84.1%. SAE were noted in a third of the patients, most commonly infections. During the trial, four patients died due to a treatment related event.

Therefore, in general for fit cHL patients older than 60 years treated with chemotherapy in curative intention, we recommend more generous use of granulocyte-colony stimulating factors to prevent infectious complications, in contrast to general recommendations for younger patients.

CONCLUSION

Therapy for fit older patients with advanced disease can consist out of two cycles of ABVD, four cycles of AVD (omission of bleomycin) and subsequently involved field radiotherapy if PET positive at end of treatment. PVAG and PVAB are interesting alternative schedules. We recommend liberate use of granulocyte-colony stimulating factors to prevent infectious complications (*Figure 2*).

FIRST LINE TREATMENT IN FRAIL PATIENTS

For frail patients with multiple comorbidities, not eligible for above-mentioned schedules, there is no well-defined standard of care. Radiotherapy only can be an option.

Another therapeutic strategy is to use vinblastine, a vinca-alkaloid known to have a relatively low toxicity. Evidence to support this strategy is limited. A recent report from a group in Bordeaux, described the interesting results of an observational retrospective mono-centric study conducted between 2010 and 2020.[17] The median age of the eleven studied patients was 85 years (range 70-89), performance score ≥ 2 in nine patients, CCI score > 6 in all patients. Vinblastine (5-6 mg/m^2) (in combination with prednisone 1 mg/kg IV) was given in first (8/11) or second line, every week or two weeks (at discretion of physician) for two months, followed by every two weeks until disease progression or unacceptable toxicity. Median duration of therapy was three months. Overall response rate was 45%, 1/11 reached a complete response. With a median follow-up of eight months, median PFS was seven months, median OS was 33 months. Overall good tolerance (mainly haematologic and neurologic toxicity), no febrile neutropenia or severe infections were reported, most of all because 64% of patients experienced clinical benefit in this palliative setting. In some patients, vinblastine improved the clinical condition, allowing for subsequent more intensive treatment.

NEW MOLECULES IN FIRST LINE TREATMENT

BRENTUXIMAB VEDOTIN (BV)

Brentuximab vedotin, an antibody-drug conjugate directed against CD30, was investigated as first line treatment in monotherapy for frail older patients ineligible for chemotherapy or declining chemotherapy treatment. A median of eight cycles was given and a CR rate of 73% was reached, however the median duration of response was only 9.1 months.[18]

In 2018, several studies were published concerning BV + chemotherapy. B-CAP (BV combined with cyclophosphamide, doxorubicine and prednisone) was tested in 49 patients, median age 61 years, and led to a 1-year PFS of 78.9%. Up to now, further follow-up results are awaited.[19]

A pre-specified sub analysis of the older patients in the ECHELON-1 trial showed that older patients did not benefit from BV-AVD and had a higher toxicity rate, in particular febrile neutropenia.[20] Median age (range) of older patients was: A+AVD, 68.0 years (60-82); ABVD, 66.0 years (60-83). One hundred and eighty six out of one thousand three hundred and thirty four patients in the intent-to-treat (ITT) population were aged ≥60 years. With median follow-up of 25 months, 2-year modified PFS was similar in both arms (A+AVD 70.3% [95% CI: 58.4, 79.4]

vs. ABVD 71.4% [95% CI: 60.5, 79.8]; HR=1.00 [95% CI: 0.58, 1.72]; p=0.993). However, the study was not powered for age-based subgroup analyses. The high incidence of febrile neutropenia in older A+AVD patients points to the need for G-CSF.

Consequential treatment with BV was tested by Evens *et al.*[21] Forty-eight patients were treated with two cycles of BV, followed by four cycles of AVD and if a partial or complete response was obtained, four additional cycles of BV were given. Results showed a 2-year PFS of 84% and OS of 93%, also in this trial grade 3/4 neutropenia was seen in almost half of the patients. Febrile neutropenia was seen in 8% of the patients.

BV was also given in combination with dacarbazine or bendamustine in a trial published by Friedberg *et al.* The combination with dacarbazine was better tolerated and yielded a CR rate of 63% with a median PFS of 17.9 months.[22]

CHECKPOINT-INHIBITORS

No major differences between young and older patients with cHL were found with regard to genetic lesions, such as the amplification of the 9p24.1 locus. This suggests that anti-programmed cell death protein 1 (PD-1) antibodies, can also be an attractive strategy in older patients.[23]

A recent phase II trial studied the combination of brentuximab vedotin (1.8 mg/kg) plus nivolumab (3 mg/kg) every 21 days for eight cycles as a chemo-free first-line treatment in older patients or younger patients unfit for chemotherapy (ACCRU trial). Thirty-five out of forty-six patients, with a median age of 71.5 years, completed all eight cycles. Forty eight percent of patients achieved a complete metabolic response and 13% a partial metabolic response. Accrual was closed because the trial did not meet its predefined criteria. Forty eight percent of patients had peripheral neuropathy, of whom 11% grade 3.[24]

In an earlier phase II trial studying the same combination, for up to sixteen cycles of 21 days, in 21 patients (majority with stage III and IV) an encouraging 72% CR and 28% PR rate was obtained, with also peripheral neuropathy being a predominant adverse event. However, small numbers, no long follow-up and these data on CR and PR were not validated in the ACCRU trial.[25]

Nivolumab in monotherapy or combination with vinblastine chemotherapy is currently studied in first line in the LYSARC driven NIVINIHO trial. Rationale, amongst others, is the hypothesis that vinblastine boosts dendritic cell maturation and might therefore be synergistic with checkpoint-inhibitors. This multicentric phase II consists of six cycles Nivolumab (two week interval) followed by a PET-CT scan. In case of CMR, patients will receive eighteen additional cycles of Nivolumab, according to CT-based response at Cycle 12. In case of PMR or No Metabolic Response (NMR), patients will receive twelve to eighteen cycles of Nivolumab combined with vinblastine (6 mg/m^2 IV) according to CT-based response at Cycle 12. In case of progressive disease, patients will be considered in treatment failure. Results are pending (NCT03580408).

RELAPSED OR REFRACTORY DISEASE

Even more challenging is treatment of relapsed/refractory disease in older patients. Although the disease itself is the most common cause of death, no prospective trials are available.

A very reasonable approach was postulated in a retrospective trial by the GHSG. One hundred and five patients were divided into high or low risk groups according to the presence of risk factors: early relapse, stage III-IV at relapse and anaemia. Patients with zero or one risk factor had a 3-year PFS of 59% and could benefit from treatment where as high risk patients only had a 3-year PFS of 9%. In the latter palliative care was proposed.[26]

From the date of the Swedish Cancer and Lymphoma Registries, we know that only 6% of the patients above 60 years proceed to high dose chemotherapy and ASCT.[27] Mostly, the goal of therapy in relapsed/refractory cHL in older patients is palliation. We should however take into account that these results are from the era before brentuximab vedotin and checkpoint-inhibitors. The hope for the future is that these novel agents might change perspectives.

No specific trials for brentuximab in R/R older patients are available. Median age in the pivotal study was only 31 years. However the treatment is probably feasible and has a high single agent activity although duration of response can be short.[28]

PD-1 blocking agents such as nivolumab and pembrolizumab have also shown high efficacy in the treatment of relapsed/ refractory Hodgkin's disease.[29,30] Also for these agents no separate data in older patients are available and only 10% of patients enrolled in registration trials were ≥ 60 years.

Recently, reimbursement of pembrolizumab from third line without previous brentuximab vedotin therapy has emerged, based on the Keynote-204 trial. Pembrolizumab showed statistically significant and clinically meaningful improvement in PFS compared with brentuximab vedotin. In this trial, 17.9% of the patients in the pembro-arm and 14.4 % of patients in the BV arm were aged > 65 years.[31]

However, recently published real-world data suggests that older patients experience more frequent adverse events: although older patients comprise 20% of the HL population

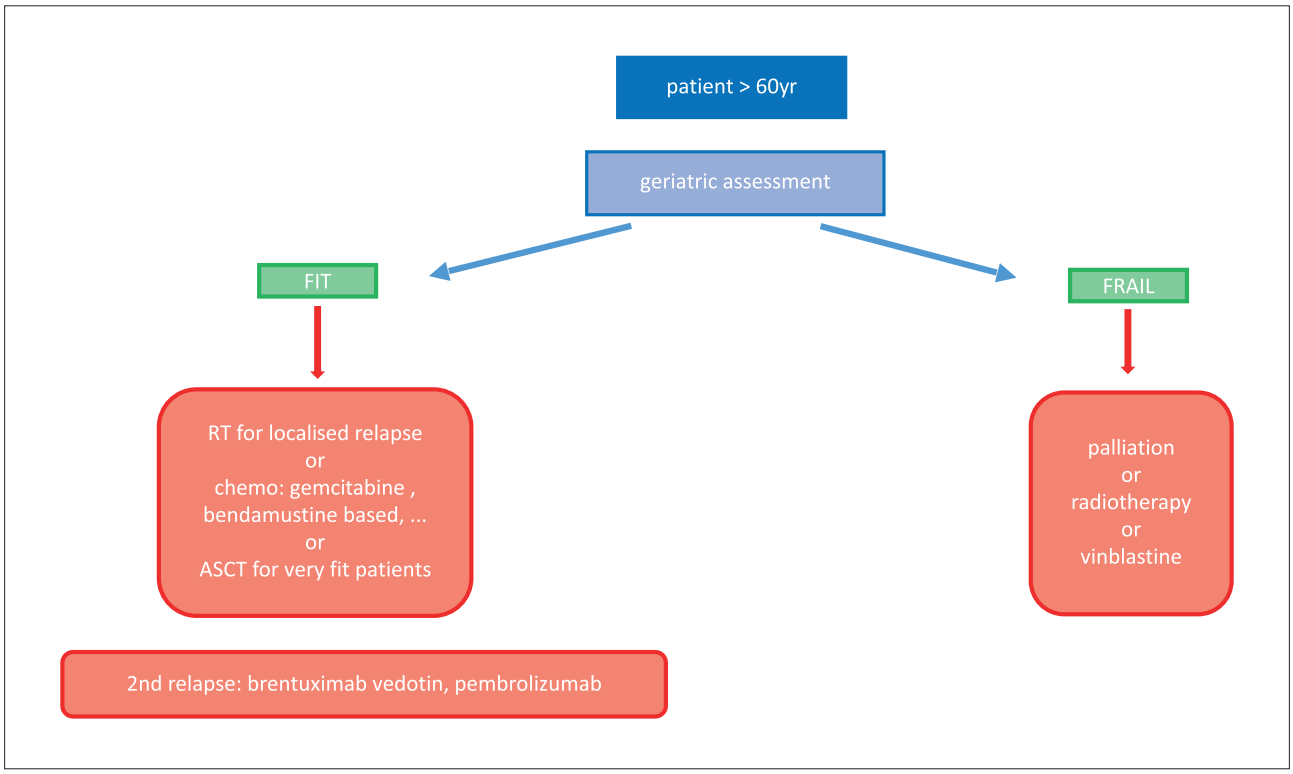

FIGURE 3. Treatment for relapse HD in older patients.

treated with checkpoint-inhibitors studied, the analysis indicates that adverse events in this subgroup account for more than 40% of total. Mainly infections and need for hospitalisation were more common.[32]

Palliative treatment schedules that can be proposed for older patients are vinblastine monotherapy, gemcitabine-containing regimens, bendamustine, *etc.* As mentioned before, evidence from clinical trials is lacking, so we cannot recommend one schedule above others.

Localised radiotherapy also might be an option if there is a localised relapse that can be captured in a radiation field.

CONCLUSION

Older, fit patients with chemo-sensitive disease, can be retreated with another multi-agent chemotherapy regimen. Radiotherapy should also be considered for localised relapse or palliative purposes. For multi-relapsed patients or chemo-refractory disease, brentuximab vedotin and checkpoint inhibitors are good options. According to Belgian reimbursement criteria, brentuximab can only be prescribed from third line on. Recently, reimbursement criteria for pembrolizumab changed as it can now also be prescribed from third line. Nivolumab is not reimbursed for older patients that were not eligible for autologous stem cell transplantation. For unfit patients, palliation is the primordial goal of therapy. Vinblastine monotherapy or best supportive care are good option in this setting (*Figure 3*).

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KEY MESSAGES FOR CLINICAL PRACTICE

1 **Hodgkin's lymphoma is difficult to treat in patients above 60 years old due to comorbidity of the patients and different disease characteristics. Patients older than 60 are often underrepresented in the clinical trials.**

2 **As first line treatment, A(B)VD, followed by IFRT in early disease, is recommended and is feasible in older patients. New treatment schedules with gemcitabine or bendamustine are of interest in advanced disease.**

3 **The incorporation of new agents such as brentuximab vedotin and checkpoint inhibitors in the treatment schedules is promising.**

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