Netherlands
The Journal of Medicine

REVIEW

Hodgkin's lymphoma: news from an old disease

J.M.M. Raemaekers[1*], R.W.M. van der Maazen[2]

Departments of [1]Haematology and [2]Radiotherapy, Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands, [*]corresponding author: tel.: +31 (0)24-361 47 62, fax: +31 (0)24-354 20 80, e-mail: J.Raemaekers@hemat.umcn.nl

KEYWORDS

Hodgkin, lymph node, lymphoma

INTRODUCTION

In 1832, Thomas Hodgkin reported a remarkable clinical condition characterised by enlargement of the lymph nodes and spleen, not compatible with known infectious disorders.[1] In 1856, Samuel Wilks published a series of 15 cases with similar features.[2] He suggested to name it Hodgkin's disease, after appreciating that Thomas Hodgkin had been the first to describe this entity. Recently, almost 150 years later, the term Hodgkin's disease was renamed Hodgkin's lymphoma (HL) according to the new World Health Organisation (WHO) classification of lymphoid neoplasms.[3] The new classification recognises the fact that this disorder belongs to the large range of malignant lymphomas.

Today, HL is one of the best curable malignancies in adult patients. The treatment has evolved from the first temporary successes with local radiotherapy (RT) via wide-field RT to a sophisticated combined modality approach of restricted chemotherapy and limited RT. However, surviving patients may suffer from long-term treatment-induced adverse effects, especially attributable to wide-field RT. Risk-adapted therapy according to prognostic factors is being tested intensively and an optimistic look to the future unveils individually tailored treatment programmes. Some of the major advances in the management of patients with HL are discussed here.

EPIDEMIOLOGY

In the Netherlands, yearly approximately 350 patients are diagnosed with HL. The incidence has been rather stable during the last decades. Some data suggest that the incidence in young adults in developing countries is rising while stabilising in Western countries.[4] Though the lowest incidence has been reported among people from Asian descent, recent data from Japan show an increasing incidence. Moreover, in Chinese immigrants in British Columbia the incidence of HL is higher than that in the Chinese population in Hong Kong, suggesting that environmental and lifestyle factors play a role in the pathogenesis.[5] The incidence in immune-compromised patients, e.g. those with organ and stem cell transplantation, and those with autoimmune diseases with their modern, intensified treatments, is rising. Remarkably, in human immunodeficiency virus infected patients the incidence of non-Hodgkin types of lymphomas is decreasing after the introduction of highly active antiretroviral therapy (HAART) while that of HL appears to rise.[6] The role of the Epstein-Barr virus (EBV) in the pathogenesis is still controversial (a detailed discussion is beyond the scope of this article). The genetic susceptibility to HL is corroborated by the almost hundredfold increased risk in identical twin siblings of a twin with Hodgkin's lymphoma.[7] Recently a polymorphism in the interleukin-12 expression regulating gene was found in co-twins of patients with HL suggesting a possible attribution to the increased Hodgkin susceptibility.[8]

PATHOLOGY

The giant multinucleated tumour cell first described by Sternberg and Reed in the early 20th century, has long obscured its origin. At present, there is no doubt that this Reed-Sternberg (RS) cell is a B-cell lymphocyte, though a peculiar one.[9] The cell does have rearranged immunoglobulin genes in line with its (post)germinal centre origin. However, the cell is largely incapable of producing immunoglobulins (Ig). It has lost typical B-cell

markers such as CD20 and CD79a, but expresses such antigens as CD15 and CD30. The expression of functional Ig genes is prevented by crippling mutations in the rearranged Ig genes, but many cases have intact rearranged genes so the crippling mutations do not represent the whole story. In addition, disturbed B-cell transcription factors are held responsible for the absence of a classic B-cell phenotype. In a 'normal' situation the defective B cells would undergo apoptosis. This Fas-mediated process is antagonised by c-flice-inhibiting protein that is overexpressed by the RS cell. Apart from this mechanism, the RS cell has a constitutive activation of nuclear factor kappa B (NFκB) leading to enhanced proliferation. A role for EBV is suggested in this respect via its activation of NFκB through CD40. Another cause for the overexpression of NFκB is a defect in the inhibitory work of inhibitory kappa B factor (IκB) especially in EBV-negative cases in which fatal mutations in the IκB gene have been demonstrated. In addition, amplifications on chromosome 2 have been found leading to activation of NFκB. All these findings shed some light on the pathogenesis of HL but much remains to be clarified. The crucial role of the abundant inflammatory infiltrate in the involved lymph node composed of T and B cells mixed with neutrophils, macrophages, eosinophils and mast cells, is being increasingly recognised. For its growth and proliferation the RS cell appears to be dependent on this network of cytokine and chemokine producing cells. The RS cells actively produce cytokines thereby attracting the immune cells.[10] Proteomics analysis of cell culture supernatants of HL cell lines revealed a possible role for such proteins as fractalkine, CD150, interleukin-25 and thymus-and-activation-regulated chemokine (TARC) amongst others. Some of the identified proteins, especially TARC, showed elevated levels in patients plasma and could well serve as a biomarker of the activity of the disease.[11] Differences between individual patients in these complex interactions may be responsible for the diversity in clinical presentation and course of the disease, opening avenues for targeted treatment approaches.

Classical HL has four histological subtypes. The nodular sclerosis variant is most common, comprising 80 to 90% of all cases, the mixed cellularity variant represents 10 to 15% of the cases, the lymphocyte-rich classical HL variant 2 to 5% and the lymphocyte-depleted ('poor') type is extremely rare. *Table 1* summarises the characteristics of the peculiar phenotype of the RS cell. Classical HL clearly differs from the nodular lymphocyte predominant type of HL (NLPHL), also known as *nodular paragranuloma*. This separate entity displays a distinct B-cell pattern, is almost always EBV negative, is most frequently localised in only one or two lymph node areas and can be treated with radiotherapy alone (*table 1*). Nevertheless, relapses occur frequently in contrast to classical HL. Especially in cases with more extensive disease and/or significant B symptoms, special awareness for the (co)-presence of a T-cell rich B-cell lymphoma or other type of B-cell non-Hodgkin's lymphoma is warranted. Suspected lesion(s) should be biopsied and even a complete extirpation of the originally involved lymph node should be considered, if it has not yet already been completely removed, in view of the major therapeutic consequences.

Table 1. *Immunohistochemical characteristics of classic Hodgkin's lymphomas (HL) vs the nodular lymphocyte predominant type (NLPHL)*

Characteristic	Classic HL	Nodular lymphocyte predominant HL (nodular paragranuloma)
Pattern	Nodular, diffuse, interfollicular	Nodular, at least partly
Tumour cells	Reed-Sternberg; mononuclear and lacunar cells	L&H/popcorn cells, scarce or no Reed-Sternberg cells
Fibrosis	Often	Rarely
CD15	+	-
CD30	+	-
CD20	-/+	+
CD45	-	+
EMA	-	+
EBV (in RS cells)	+ (50%)	-
Ig genes	Rearranged, clonal, fatal mutations, no/few Ig	Rearranged, clonal, ongoing mutations, Ig production

L&H = lymphocyte and histiocyte; EMA = epithelial membrane antigen; EBV = Epstein Barr virus; Ig = immunoglobulin.

IMAGING

The most important development in the imaging of HL is the 2-^{18}F-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) scan. Conventional staging is still based on computed tomography scans combined with clinical information and histological bone marrow examination resulting in the Ann Arbor stage (I-IV) of the disease. The FDG-PET scan is based on the principle that malignant tumours have increased uptake of glucose compared with normal tissue. No large series are available to precisely define sensitivity and specificity in the staging of HL because of the lack of comparison with the golden standard, e.g. histological proof of suspected lesions.[12,13] One step ahead is the combined FDG-PET/CT technique that provides anatomical correlates on CT for positive FDG-PET findings, thereby probably increasing its reliability. Hutchings *et al.* reported upstaging of 17% and downstaging of 5% in a series of 61 patients using combined FDG-PET/CT.[14] Thanks to improvements in CT imaging and the additional CT-PET techniques, Ann Arbor stage I/II disease in 2008 is not identical to the stage I/II in 1970. The FDG-PET scan has already been

introduced into clinical practice without a rigorous testing of its precise role. The key issue is whether a change in staging modifies the treatment that should be given and whether such change leads to a better outcome. In patients with stage I/II disease the extent of the RT fields can be influenced, and in patients moving from early to advanced stages more prolonged chemotherapy would be instituted. In Hutchings *et al.'s* series, the stage migration would have resulted in a change in treatment in only 7% of the patients (all moved from early to advanced stage).[14] Nevertheless, we should recognise that FDG-PET scans will be increasingly used in the staging of patients and will lead to adaptations in the clinical management of the patients.

The more so, since new international guidelines for assessment of response to therapy in HL have been published.[15] In these response criteria, a FDG-PET scan response assessment is mandatory to evaluate the response at the end of treatment. Preferably, this FDG-PET scan should be performed four to six weeks after completion of treatment to avoid false-positive results. Though a pretherapeutic scan is not mandatory according to the guidelines, it is strongly recommended since the post-treatment interpretation of response by FDG-PET is facilitated by comparison with a pretherapeutic scan. So, we do need a FDG-PET scan at the start of treatment as well. The exciting prospects of interim response assessment (after two to three cycles of chemotherapy) by FDG-PET scan are discussed under Current and future directions.

We should keep in mind that the interpretation of an FDG-PET scan requires experienced nuclear medicine physicians and a multidisciplinary clinical consultation round. If PET-positive lesions are not recognised earlier on CT scans, the CT scans should be revised looking for an anatomical substrate for the PET-positive lesions. If not evident, the lesion should not be automatically considered as tumour positive and a histological biopsy specimen of the suspected area should seriously be considered.

CHEMOTHERAPY

The combination of doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) is the current standard chemotherapy (*table 2*). The development of ABVD stems from the 1970s,[16] but it was the result of the Intergroup randomised trial comparing ABVD with hybrid MOPP/ABV (mechlorethamine, vincristine, procarbazine, prednisone/ doxorubicin, bleomycin, dacarbazine), published in 2003, that established ABVD as the preferred treatment.[17] Although there was no significant difference in efficacy between the two treatment arms with a five-year freedom-from-treatment failure (FFTF) rate of 63 *vs* 66% and an overall survival (OS) of 82 *vs* 81% respectively, the second malignancy rate was higher in the hybrid arm, favouring the use of ABVD. In addition, the switch from the classic alkylating agent-based MOPP or MOPP-like regimens to the anthracycline-based ABVD and its variants reduces the risk of infertility. Nevertheless, ABVD is far from perfect. Dacarbazine is highly emetic and can cause severe phlebitis. Bleomycin gives rise to pulmonary toxicity with occasional, but consistently occurring, pulmonary toxic deaths. Last but not least, 25 to 35% of patients with advanced disease fail to respond to ABVD and will require intensive salvage treatment with uncertain outcome. Diehl and the German Hodgkin Study Group (GHSG) developed a dose-intense multidrug regimen.[18] The resulting dose-escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone (BEACOPP) schedule was designed to significantly increase early remission rates and to decrease the frequency of primary progressive and relapsing disease (*table 2*). There is no doubt that this regimen is one of the most active drug combinations, with an 82% FFTF and 86% OS at ten years. However, this regimen is not only anthracycline-based but includes alkylating agents as well. Thus, we will encounter untoward effects of the latter, such as second leukaemias and infertility. This has led to adaptations to the original escalated BEACOPP regimen. An initial four cycles of escalated dosed BEACOPP followed by four cycles of baseline-dosed BEACOPP appears to be as effective as the eight cycles of escalated BEACOPP, as suggested by the preliminary analysis of the GHSG HD12 study.[19] In the recently completed GHSG HD15 study, eight

Table 2. *Doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) and bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone (BEACOPP) chemotherapy*

ABVD (cycle length 28 days)

Drug	mg/m²	Route	Days
Doxorubicin	25	iv	1 and 15
Bleomycin	10	im/iv	1 and 15
Vinblastine	6	iv	1 and 15
Dacarbazine	375	iv	1 and 15

BEACOPP (cycle length 21 days)

Drug	mg/m²		Route	Days
	Baseline	Escalated		
Bleomycin	10	10	im/iv	8
Etoposide	100	200	iv	1, 2, 3
Doxorubicin	25	35	iv	1
Cyclophosphamide	650	1250	iv	1
Vincristine	1.4 (max. 2.0)	1.4 (max. 2.0)	iv	8
Procarbazine	100	100	orally	1-7
Prednisone	40	40	orally	1-14
G-CSF		+	sc	8+

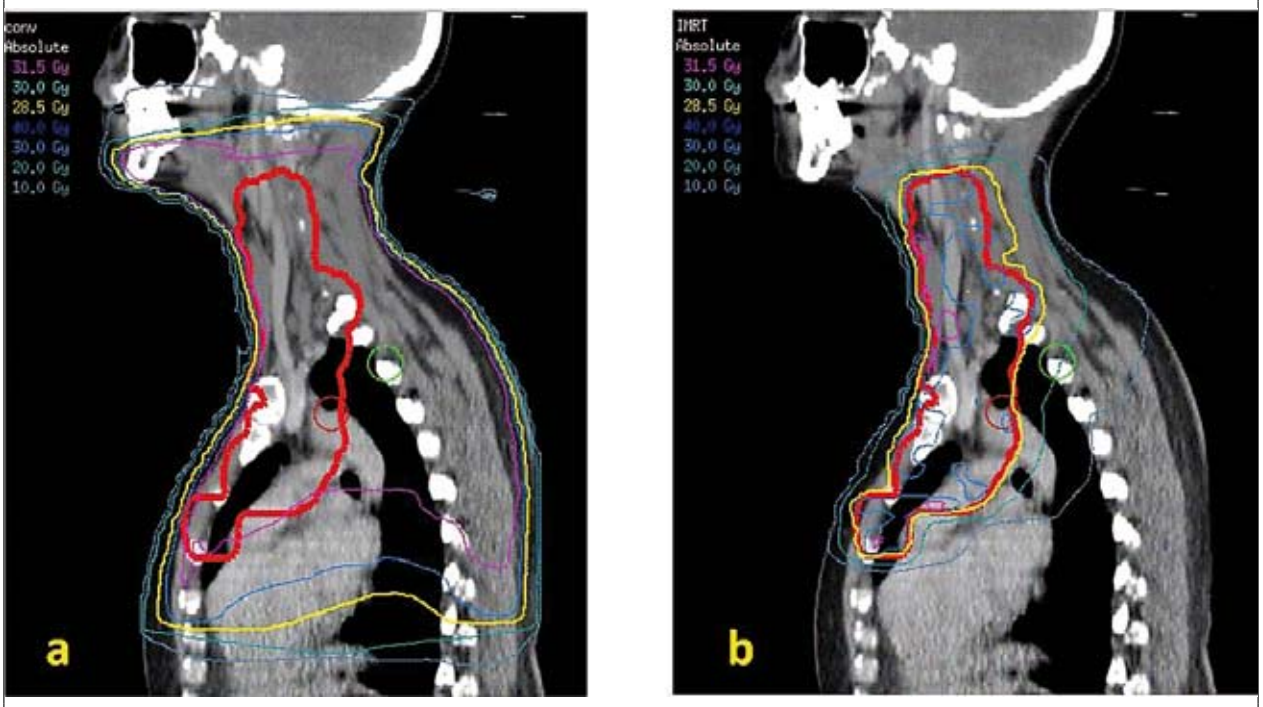
G-CSF = granulocyte-colony stimulating factor: dose dependent on product given.

cycles of escalated BEACOPP were randomly compared with six cycles of the same regimen and with eight cycles of BEACOPP14, the latter being a BEACOPP variant with baseline doses but given at a 14-day rather than 21-day interval. Results have to be awaited, especially with regard to toxicity.

RADIOTHERAPY

Radiotherapy is still the most efficacious single-agent treatment of HL. But the successful wide-field applications such as mantle field, inverted Y or (sub)total nodal irradiation, have their price in terms of second infield malignancies, and cardiovascular complications.[20] Combination chemotherapy eradicates not only clinically evident but also microscopic disease. Therefore, the large RT fields could be reduced to what are known as involved fields, e.g. only the initially involved lymph node areas, in the setting of combined modality treatment consisting of chemotherapy plus RT. As a result, the prophylactic irradiation of presumably unaffected nodal areas became redundant. In appreciating the high efficacy of chemotherapy, RT can probably be reduced even further. Better imaging techniques including 3D CT scan and FDG-PET scan allow more precise targeting and modelling of RT. Girinsky *et al*. have nicely demonstrated the potentials of reduction of the involved field principle to the involved node technique in which only the initially involved nodes rather than the involved field are being irradiated.[21,22] *Figure 1* shows the reduction in delivered RT to a neck nodal mass when irradiated according to the IF-RT technique compared with the IN-RT principle. This approach with allegedly less toxicity is now being applied in the current Intergroup H10 study of the EORTC Lymphoma group, the Groupe d'Etudes des Lymphomes de l'Adulte (GELA) and the Intergruppo Italiano di Linfomi (IIL) (see later under Current and future directions). Although attractive, a special note of warning should sound. By reducing the RT field, the exact localisation of the initially involved lymph nodes has become crucial, for the remaining nodes in the respective lymph node area will not be irradiated. Here, we need – more than ever – a close multidisciplinary cooperation between radiation oncologist, haematologist, radiologist, and nuclear medicine physician to exactly define the targets of treatment. A judicious interpretation of combined FDG-PET/CT scan imaging will probably help to come up to our expectations of a safe reduction in RT fields.

Figure 1. *Sagittal view of a patient with clinical stage II Hodgkin's lymphoma with localisations in neck and mediastinum*



The thick red line encompasses the pre-chemotherapy involvement with a 1 cm margin. The CT scan is taken for radiotherapy treatment purposes after chemotherapy.
A) Dose distribution when the patient is irradiated according to the involved field principle.
B) Dose distribution when the patient is irradiated according to the involved node principle with an intensity modulated radiotherapy technique. Notice that the coverage of the target volume (red contour) in both plans is good (yellow line, 95% of prescribed dose). The involved node technique gives a considerable sparing of normal tissues (heart, lung, neck, mouth).

SURVIVORSHIP

In appreciating survivorship for patients treated in the modern era, we should take into account that our knowledge of long-term complications is based upon observations after extended-field RT and alkylating chemotherapy regimens. Second malignancies mainly concern breast and lung cancer. Female patients who received RT to mediastinal and/or axillary nodes prior to the age of 30 have a 2.5 to >5 times elevated risk of developing breast cancer.[23] The risk appears to be most pronounced in women who remain premenopausal for >15 years after treatment for HL, whereas those who became postmenopausal within five years after treatment had a significantly lower risk of secondary breast cancer.[24] The protective effect of (alkylating) chemotherapy-induced menopause will probably disappear with increasing use of the more ovary-friendly ABVD. Elevated risks of lung cancer are reported after RT but also after alkylating agents while smoking even further increases the relative risk to >9.[25,26] A recent Dutch cohort study estimated a three to fivefold increased incidence of several types of cardiac diseases after RT and anthracycline-containing chemotherapy compared with the general population, with the highest risks observed in the youngest patients at diagnosis of HL.[27,28] Patients irradiated to the neck have an increased risk of stroke.[29] Male infertility has been recently readdressed by the GHSG and the large series of the EORTC highlighting the high incidence of >93% of elevated FSH levels after alkylating agents, especially BEACOPP,[30] *vs* only 8% after ABVD.[31]

Awareness of these late effects urges the need for guidelines for standardised follow-up examinations in long-term survivors. The yearly mammographic examinations for female patients irradiated at young age is already standard and starts eight to ten years after RT. According to the Dutch guidelines an MRI should be performed as well for screening in this high-risk group of patients. Yearly thyroid-stimulating hormone measurements for detection of irradiation-induced hypothyroidism is done in most patients. The relevance of screening and/or early intervention strategies for cardiovascular diseases is less evident and awaits further research.

HOW TO MANAGE?

Favourable Ann Arbor stage I/II

In patients with stage I/II disease we can identify a subset with favourable pretreatment criteria (40 to 45% of patients) and a group with unfavourable characteristics (55 to 60%) (*table 3*). The cornerstone of the treatment for patients with stage I/II HL is the combined modality approach. On behalf of the EORTC and GELA, Fermé *et al*. reported in 2007 on the H8 trial for patients with stage I/II HL.[32] Patients with favourable stages I/II were randomised between subtotal nodal irradiation (the standard treatment at the time the trial started in 1993) and the combined modality regimen consisting of three cycles of MOPP/ABV hybrid (the standard chemotherapy at the time the trial started) followed by 36 Gy involved-field RT (IF-RT). After a median follow-up of 92 months the combined modality treatment proved superior, not only in terms of event-free survival (EFS) but also in terms of OS: at ten years an EFS of 68 *vs* 93% and an OS of 92 *vs* 97% respectively (p=0.001). Excellent results for sure, but how should these data be handled in 2008? MOPP/ABV hybrid is no longer standard chemotherapy because of the increased risk of secondary leukaemias and infertility. ABVD should be given instead. But in this limited disease situation, even three cycles of ABVD might be too toxic. In the most recent GHSG HD13 study the relative merits of the individual components of the ABVD regimen have been randomly compared, e.g. two cycles of ABVD *vs* AVD *vs* ABV *vs* AV. Can bleomycin be removed from the ABVD regimen? This is the crucial question but final results are not yet available.

Whereas the chemotherapy adaptations seem to reach a final endpoint quite soon, the radiotherapy component of the combined modality is being adapted as well. There are some preliminary data that suggest that the dose of RT can be reduced from 30-36 to 20 Gy. However, both in the EORTC/GELA H9 study and in the GHSG HD10 study, the FFTF curves of the 30-36 Gy *vs* those of 20 Gy appear to diverge in favour of the higher dose of RT after prolonged follow-up periods of more than six years.[33,34] Since the extremes in the Kaplan-Meier survival curves should be interpreted with caution, no final conclusion can

Table 3. *Definition of favourable and unfavourable stage I/II Hodgkin's lymphoma*

	European Organisation for Research and Treatment of Cancer	German Hodgkin Study Group
Risk factors	a) Large mediastinal mass b) Age ≥50 years c) ESR ≥50 without B symptoms or ≥30 with B symptoms d) ≥4 nodal areas	a) Large mediastinal mass b) Extranodal disease c) ESR ≥50 without B symptoms or ≥30 with B symptoms d) ≥3 nodal areas
Favourable	CS I-II (supradiaphragmatic) without any risk factor	CS I-II without any risk factor
Unfavourable	CS I-II (supradiaphragmatic) with at least 1 risk factor	CS I or CS IIA with at least 1 risk factor CS IIB with c) or d) but without a) and b)

ESR = erythrocyte sedimentation rate; LP = lymphocyte predominance; NS = nodular sclerosis; CS = clinical stage.

be drawn yet from these large randomised trials. A dose of 30 Gy is still standard. Can RT be omitted in the early-stage situation? The answer is no. In the EORTC/GELA H9F trial randomising between no RT after six cycles of the ABVD chemotherapy variant EBVP (epirubicin, bleomycin, vinblastine, prednisone)[35] and IF-RT, the no-RT arm had to be closed prematurely because of a significantly higher incidence of relapses/progressions compared with the RT arms.[33] The conclusion from this H9F trial is that RT cannot be omitted after EBVP chemotherapy in favourable stage I/II disease. That does not necessarily mean that RT is always required after other chemotherapy such as ABVD, but this question should be readdressed in a randomised clinical trial as is being done in the H10 trial (see below). In the meantime the combined modality approach remains standard treatment for favourable stages I/II.

Unfavourable Ann Arbor stage I/II

In the abovementioned EORTC/GELA H8 study the patients with unfavourable stages I/II were randomised between three different combined modality approaches: six cycles of MOPP/ABV + 36 Gy IF-RT *vs* four cycles of MOPP/ABV + 36 Gy IF-RT *vs* four cycles of MOPP/ABV + 36 Gy subtotal nodal irradiation.[32] After a median follow-up of 92 months no differences between the three treatment arms were seen, neither in EFS nor in OS (around 85%). In this subset of patients there is room for improvement of tumour control. In an attempt to improve the outcome, the successor EORTC/GELA H9 trial randomly compared four cycles of ABVD to four cycles of baseline dose BEACOPP, both followed by 30 Gy IF-RT. In the first preliminary analysis no significant differences in outcome were noted.[33] Similarly the GHSG HD11 trial failed to show an improvement in outcome after baseline-dosed BEACOPP as compared with ABVD in this subset of patients.[19] Therefore, the combined modality consisting of four cycles of ABVD followed by 30 Gy IF-RT remains the standard treatment.[36]

Ann Arbor stage III/IV

Patients with advanced disease receive six to eight cycles of ABVD. In case of a CR after chemotherapy, additional RT is not required as shown in the EORTC 20884 trial.[37] In case of residual disease after six cycles of chemotherapy additional involved field RT is given. With this strategy a seven-year FFTF of >70% and OS of >80% have been reached.[38]

In the landmark GHSG HD9 randomised clinical trial, 1186 evaluable patients have been randomised between the ABVD variant COPP/ABVD, the baseline-dosed BEACOPP and the escalated-dosed BEACOPP schedule.[18] Most patients received additional 30 Gy RT to initially bulky masses (defined as >5 cm) or residual disease after chemotherapy. The initially reported significantly better outcome for patients treated with escalated BEACOPP still holds after prolonged follow-up: at ten years FFTF are 64% (COPP/ABVD), 70% (BEACOPP baseline) and 82% (escalated BEACOPP) and OS rates of 75, 80 and 86% respectively. The hypothesis of avoidance of early treatment resistance by starting with the dose-intense regimen right away appears to be corroborated by the differences in induction failure rates between the three treatment arms: 25, 12 and 4% respectively. The results also suggest that escalated BEACOPP should become the new standard chemotherapy schedule instead of ABVD. However, some reticence is justified. The schedule is manageable but toxic. It requires haematopoietic growth factor support, more frequent day care facilities because of the administration schedule of the chemotherapy, it includes alkylating agents with the increased risk of infertility and second leukaemias, and last but not least, awaits confirmation of its supposed enhanced efficacy from other randomised trials. One of these trials, the Italian cooperative group HD2000 GISL study, was recently reported in a preliminary analysis.[39] A three-arm comparison was made between six cycles of ABVD, COPPEBVCAD and BEACOPP (first four cycles in escalated dose followed by two cycles in baseline dose). RT was delivered to initially bulky or residual masses. The analysis on 270 evaluable cases showed no statistically significant differences in CR rates after chemotherapy: 82, 79 and 90% respectively. After a median follow-up of 39 months, the three-year progression-free survival was significantly better for the BEACOPP arm as compared with ABVD and COPPEBVCAD: 90 *vs* 72 *vs* 80% respectively. No significant differences in OS were observed. The BEACOPP regimen was associated with higher rates of severe infections, 13 *vs* 1 and 3% respectively. No definite conclusions can be drawn yet. Therefore, the results of the ongoing Intergroup trial 20012 led by the EORTC, randomly comparing eight cycles of ABVD with four cycles of escalated-dosed BEACOPP followed by four cycles of baseline-dosed BEACOPP, are eagerly awaited. This study addresses the 'poor-risk group' of advanced stage patients, e.g. those with an International Prognostic Score of >2 factors (*table 4*).[40] Details on the frequency distribution of the patient numbers and their respective outcome dependent on the number of adverse factors are also given in *table 4*. In contrast to the GHSG and the Italian study, in the EORTC trial no RT is given to patients who reach a CR on chemotherapy.

Another remarkable issue in comparing ABVD and escalated BEACOPP should be taken into account, as Horning correctly pointed out in the 2007 educational session of the American Society of Hematology.[41] One of the presumed reasons for the success of escalated BEACOPP is the increased dose intensity pushed to the limit by support of haematopoietic growth factors. All studies with ABVD are based upon the rather conservative

Table 4. *International Prognostic Score for patients with stages III/IV Hodgkin's lymphoma*

Number of factors	% of patients	5-year progression-free survival %
0	7	84
1	22	77
2	29	67
3	23	60
4	12	51
≥5	7	42

The seven clinical prognostic factors are: age ≥45 years; male sex; Ann Arbor stage IV disease; albumin <40 g/l; haemoglobin <6.5 mmol/l; leucocyte count ≥15 x 10^9/l; lymphocyte count <0.6 x 10^9/l.

dose adaptation guidelines from the original reports resulting in frequent dose adaptations and/or delay in starting new cycles. Recent data show that ABVD can be given at 100% dosage despite neutropenia and without growth factor support.[42] In a single centre experience, two physicians treated their patients (n=61) with ABVD in full doses irrespective of neutrophil counts. The overall dose intensity was 99.1%. The incidence rate of febrile neutropenic episodes was only 0.4% in a total of 682 ABVD administrations, but – admittedly – under coverage of pneumocystis and *Candida* prophylaxis. The five-year EFS and OS for this group of patients (57% early stage and 43% advanced stages), was 93 and 97% respectively. Why these data? The question arises whether comparison of the outcome after a conservative dose-adaptation guided ABVD schedule and that after the escalated BEACOPP schedule is fair. Could the results of ABVD improve just by a full-dose strategy, despite neutropenia? If so, one could avoid the toxicity of the alkylating agents in the BEACOPP schedule. This has not been tested so far. Possibly, the abovementioned ongoing EORTC Intergroup study will shed some light on this issue.

Therefore, ABVD is still the standard chemotherapy for advanced stage patients. RT is only indicated in case of PR after chemotherapy. One probably should give the full dose of ABVD despite neutropenias. The subgroup of patients to benefit from the intense escalated BEACOPP still needs to be defined.

CURRENT AND FUTURE DIRECTIONS

Risk-adapted approaches are being explored intensively in current randomised clinical trials, in pursuit of the balance between cure and complication-free survivorship. Two main questions arise. First, do we have new reliable and reproducible indicators for risk adaptation of our treatment? We cannot expect that after so many examples of clinical prognostic indices, any new clinical pretreatment prognostic variable will be identified. Treatment-related factors are probably more informative. Old data indicated that patients with an early response to chemotherapy, e.g. CR after two to four cycles of chemotherapy, have a better outcome. In fact, the EORTC approach administering a total of only six cycles of chemotherapy in advanced stages in case of an early CR (after four cycles) and a total of eight cycles in case of late CR (after six cycles) is based on these data.[43,44]

The definition of a CR based on conventional imaging is troublesome in HL. FDG-PET imaging will probably help us out. In the new criteria for assessment of response after completion of treatment, a CR[15] implicates a negative PET scan for all lesions whereas a PR indicates a decrease of >50% of the lesions with a least one PET-positive lesion. In the recently completed GSHG HD15 trial for patients with advanced stages, only those with a PR based on conventional imaging but still PET positive receive additional RT. Final results have to be awaited. The spectacular results of the combined Italian and Danish experience with the predictive value of an early interim FDG-PET scan in patients with advanced disease hold great promise.[45] Patients received a predefined treatment, usually six to eight cycles of ABVD, followed by RT. After two cycles of chemotherapy an FDG-PET scan was performed but no treatment changes were allowed on the basis of the PET results. Fifty out of 260 patients (20%) were FDG-PET positive after two cycles of chemotherapy and 210 (80%) already FDG-PET negative. After a relatively short follow-up of two years, 43/50 (86%) of the PET-positive patients progressed or relapsed whereas only ten of the 210 PET negatives (5%) progressed or relapsed (p<0.001). It is almost too good to be true!

Second, is there any evidence to support a strategy of escalating treatment when needed, or de-escalating treatment when possible, based on the early PET response? The answer is no. Should all patients with advanced disease start with the intensive escalated BEACOPP regimen and then have a decrease in intensity in case of an early negative PET scan? Such an approach would integrate the theoretical advantage of avoiding early treatment resistance by treating as intensively as possible right from the start and by reducing the burden of subsequent treatment based on early PET response. Probably, a majority of patients would not have needed the two intensive escalated BEACOPP cycles and would have done well with ABVD, thereby avoiding the toxicity of the intensified treatment. The opposite approach is to start with a less intense treatment – for example ABVD – and to escalate in case of a positive early FDG-PET scan. This attitude would spare the initial toxicity of escalated BEACOPP but harbours the theoretical risk of having induced resistance that cannot be overcome anymore by switching to escalated BEACOPP.

We are dealing with theoretical – though plausible – assumptions and their validity should and can only be addressed in carefully designed randomised trials. *Table*

Table 5. *Current and forthcoming randomised trials in untreated patients with Hodgkin's lymphoma*

Trial	Patient groups	Trial design and randomised treatments
NCRN UK (*start 2003*)	IA/IIA, no mediastinal bulk	ABVD x 3, then PET response, • if PET negative: A. IF-RT B. no further treatment • if PET positive C. ABVD x 1 + IF-RT
EORTC/GELA/IIL H10 stage I/II (EORTC #20051) (*start 2006*)	I/II favourable	A. ABVD x 3 + IN-RT B. ABVD x 2, then PET response, • if PET negative: ABVD x 2, no RT • if PET positive: esc. BEACOPP x 2 + IN-RT
	I/II unfavourable	C. ABVD x 4 + IN-RT D. ABVD x 2, then PET response, • if PET negative: ABVD x 4, no RT • if PET positive: esc. BEACOPP x 2 + IN-RT
GHSG HD 16 (*projected start 2008*)	I/II, no risk factors	A. ABVD x 2 + IF-RT B. ABVD x 2, then PET response, • if PET negative: no further treatment • if PET positive: IF-RT
GHSG HD 17 (*projected start 2008*)	I/II, with risk factors	A. ABVD x 4 + IF-RT B. ABVD x 4 + IN-RT C. EACOPP(14) x 4 + IF-RT D. EACOPP(14) x 4 + IN-RT
EORTC Intergroup #20012 (*start 2002*)	III/IV poor risk (>2 risk factors IPS)	A. ABVD x 8 B. esc. BEACOPP x 4 + base BEACOPP x 4
GHSG HD 18 (*projected start 2008*)	III/IV	Escalated BEACOPP x 2, then PET response, • if PET negative: A. esc. BEACOPP x 6 B. esc. BEACOPP x 2 • if PET positive: C. esc. BEACOPP x 6 D. esc. BEACOPP x 6 + rituximab

NCRI UK = National Cancer Research Network United Kingdom; EORTC = European Organisation for Research and Treatment of Cancer; GELA = Groupe d'Etudes des Lymphomes de l'Adulte; IIL = Intergruppo Italiano di Linfomi; GHSG = German Hodgkin Study Group; HD = Hodgkin's disease; I/II/III/IV = Ann Arbor stages; IPS = International Prognostic Score; ABVD = doxorubicin, bleomycin, vinblastine, dacarbazine; BEACOPP = bleomycin, etoposide, Adriamycin, cyclophosphamide, vincristine, procarbazine, prednisone; esc. =escalated; IF-RT = involved field radiotherapy; IN-RT = involved-node radiotherapy; PET = positron emission tomography.

5 summarises the leading, currently ongoing or soon to be started European initiatives. In the UK trial, the main question is whether RT can be omitted in patients with stage I/II disease without mediastinal bulk, if the PET scan has become negative after three cycles of ABVD. Importantly, this randomised trial uses the PET scan at the end of chemotherapy and does not test early PET scan-guided treatment adaptation. The concept of early treatment adaptation in patients with stage I/II disease is being tested in the EORTC/GELA/IIL Intergroup H10 trial (EORTC #20051). In this important ongoing trial patients are randomised between the standard combined modality treatment (ABVD x three followed by IN-RT for the favourable subset and ABVD x four followed by IN-RT for the unfavourable subset) and the new, early PET response adapted approach: those with a negative early PET scan (after two cycles) receive additional cycles of ABVD without IN-RT, and those with a positive early PET scan switch to the intensified escalated BEACOPP schedule followed by IN-RT. In this trial, over 1500 patients are required to demonstrate that chemotherapy alone is non-inferior to the combined modality approach in case of early PET negativity and that intensification produces better results in case of early PET positivity. The target accrual is expected to be completed in 2010, with most of Dutch centres participating actively.

The GHSG will start their new-generation studies in 2008. In patients with stage I/II disease without risk factors, patients are randomised between ABVD x 2 followed by IF-RT and ABVD x 2 without RT in case of a negative PET scan after two cycles (GHSG HD16 trial). In this design a negative PET scan after two cycles of ABVD is considered synonymous to cure but it remains to be seen whether two cycles of ABVD is sufficient treatment for stage I/II disease. In stage I/II with risk factors, the randomisation concerns a four-arm comparison between four cycles of ABVD and EACOPP (a variant of the escalated BEACOPP schedule without bleomycin and given every 14 days) followed by either IF-RT or IN-RT, the only trial comparing the IF-RT principle with the concept of IN-RT (GHSG HD 17 trial). The already mentioned ongoing Intergroup trial led by EORTC for

patients with poor-risk advanced disease comparing ABVD with escalated BEACOPP is of paramount importance in defining the standard chemotherapy schedule. This study does not incorporate PET-based decisions. In the four-arm GHSG HD18 trial all patients will start on escalated BEACOPP. Those with a negative early PET scan will go on with either the standard six cycles of escalated BEACOPP or just two additional cycles aiming at reducing toxicity in a presumed good-prognosis group. Those with an early positive FDG-PET scan will continue with the standard six cycles of escalated BEACOPP or will receive the experimental arm containing six cycles of escalated BEACOPP + rituximab, the monoclonal anti-CD20 antibody, aiming at improving efficacy by targeting the presumably CD20-positive Hodgkin stem cell, in this poor-risk group.

EPILOGUE

The avenue is opened to a risk-adapted and individualised treatment approach for patients with HL. A meticulous search for the balance between cure and toxicity is the challenge for future cooperative Intergroup efforts reflected in carefully designed randomised clinical trials. The combination of chemotherapy and radiotherapy for those who need it, chemotherapy alone if possible to avoid RT-induced late complications and intensified chemotherapy BEACOPP-like regimens reserved for those with well-defined poor-risk disease.[46] The prognosis for the small subset of patients with refractory disease is still grim and urgently awaits new effective drugs possibly acting by different pathways. New strategies for elderly patients are needed as well. Continued special attention for long-term observation remains warranted to monitor whether our current concepts indeed translate into improved survivorship. Evidence-based guidelines would be helpful in offering state-of-the-art follow-up care. The momentum is here for a national initiative integrating the evaluation of early interventions for prevention and management of complications.

REFERENCES

1. Hodgkin T. On some morbid appearances of the absorbent glands and spleen. Med Chir Trans. 1832;17:69-97.
2. Wilks S. Cases of lardaceous disease and some allied affections with remarks. Guy's Hosp Rec. 1856;2:103-32.
3. Jaffe ES, Harris NL, Stein H, et al. Pathology and genetics of tumours of haematopoietic and lymphoid tissues. WHO classification of tumors. Lyon: IARCPress, 2001.
4. Macfarlane GJ, Evstifeeva T, Boyle P, et al. International patterns in the occurrence of Hodgkin's disease in children and young adults. Int J Cancer. 1995;61:165-9.
5. Au WY, Gascoyne RD, Gallagher RE, et al. Hodgkin's lymphoma in Chinese migrants to British Columbia: a 25 year survey. Ann Oncol. 2004;15:626-30.
6. Biggar RJ, Jaffe ES, Goedert JJ, et al. Hodgkin lymphoma and immunodeficiency in persons with HIV/AIDS. Blood. 2006;108:3786-91.
7. Mack TM, Cozen W, Shibata DK, et al. Concordance for Hodgkin's disease in identical twins suggesting genetic susceptibility to the young-adult form of the disease. N Engl J Med. 1995;332:413-8.
8. Cozen W, Gill PS, Salam MT, et al. Interleukin-2, interleukin-12, and interferon-alpha levels and risk of young adult Hodgkin lymphoma. Blood. 2008;111:3377-82.
9. Thomas RK, Re D, Wolf J, Diehl V. Hodgkin's lymphoma - molecular biology of Hodgkin and Reed-Sternberg cells. Lancet Oncology. 2004;5:11-8.
10. Enblad G, Molin D, Glimelius I, Fisher M, Nilsson G. The potential role of innate immunity on the pathogenesis of Hodgkin's lymphoma. Hematol Oncol Clin N Am. 2007;21:805-23.
11. Ma Y, Visser L, Roelofsen H, et al. Proteomics analysis of Hodgkin lymphoma: identification of new players involved in the cross-talk between HRS cells and infiltrating lymphocytes. Blood. 2008;11:2339-46.
12. Burton C, Ell P, Linch D. The role of PET imaging in lymphoma. Br J Haematol. 2004;126:772-84.
13. Kwee ThC, Kwee RM, Nievelstein RAJ. Imaging in malignant lymphoma: a systematic review. Blood. 2008;111:504-16.
14. Hutchings M, Loft A, Hansen M, et al. Positron emission tomography with or without computed tomography in the primary staging of Hodgkin's lymphoma. Haematol. 2006;91:482-9.
15. Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. J Clin Oncol. 2007; 25:579-86.
16. Bonadonna G, Zucali R, Monfardini S, De Lena M, Uslenghi C. Combination chemotherapy of Hodgkin's disease with adriamycin, bleomycin, vinblastine and imidazole carboxamide versus MOPP. Cancer. 1975;36:252-9.
17. Duggan D, Petroni G, Johnson J, et al. A randomized comparison of ABVD and MOPP/ABV hybrid for the treatment of advanced Hodgkin's disease: report from an Intergroup trial. J Clin Oncol. 2003;21:607-14.
18. Diehl V, Franklin J. Pfreundschuh M, et al. Standard and increased-dose BEACOPP chemotherapy compared with COPP/ABVD for advanced Hodgkin's disease. N Engl J Med. 2003;348:2386-95.
19. Diehl V, Engert A, Re D. New strategies for the treatment of advanced-stage Hodgkin's lymphoma. Hemat Oncol Clin N Am. 2007;21:897-914.
20. Aleman BMP, van Leeuwen FE. Are we improving the long-term burden of Hodgkin's lymphoma patients with modern treatment. Hemat Oncol Clin N Am. 2007;21:961-75.
21. Girinsky T, Pichenot C, Beaudre A, et al. Is intensity-modulated radiotherapy better than conventional radiation treatment and three dimensional conformal radiotherapy for mediastinal masses in patients with Hodgkin's disease, and is there a role for beam orientation optimization and dose constraints assigned to virtual volumes. Int J Radiat Oncol Biol Phys. 2005;64:218-26.
22. Girinsky T, van der Maazen MR, Specht L, et al. Involved-node radiotherapy (INRT) in patients with early Hodgkin lymphoma: concepts and guidelines. Radiother Oncol. 2006;79:270-7.
23. Van Leeuwen FE, Klokman WJ, van 't Veer MB, et al. Long-term risk of second malignancy in survivors of Hodgkin's disease treated during adolescence or young childhood. J Clin Oncol. 2000;18:487-97.
24. Van Leeuwen FE, Klokman WJ, Stovall M, et al. Roles of radiation dose, chemotherapy, and hormonal factors in breast cancer following Hodgkin's disease. J Natl Cancer Inst. 2003;95:971-80.
25. Travis LB, Gospodarowicz M, Curtis RE, et al. Lung cancer following chemotherapy and radiotherapy for Hodgkin's disease. J Natl Cancer Inst. 2002;94:182-92.
26. Van Leeuwen FE, Klokman WJ, Stovall M, et al. Roles of radiotherapy and smoking in lung cancer following Hodgkin's disease. J Natl Cancer Inst. 1995;87:1530-7.

27. Aleman BMP, van Belt-Dusebout AW, Klokman WJ, van 't Veer MB, Bartelink H, van Leeuwen FE. Long-term cause specific mortality of patients treated for Hodgkin's disease. J Clin Oncol. 2003;21:3431-9.

28. Bowers DC, McNeil DE, Liu Y, et al. Stroke as a late treatment effect of Hodgkin's disease: a report from the Childhood Cancer Survivor study. J Clin Oncol. 2005;23:6508-15.

29. Van Rijswijk S, Huijbregts MAJM, Lust E, Strack van Schijndel RJM. Mini review on cardiac complications after mediastinal irradiation for Hodgkin lymphoma. Neth J Med. 2008;66:234-7.

30. Sieniawski M, Reineke Th, Nogova L, et al. Fertility in male patients with advanced Hodgkin lymphoma treated with BEACOPP: a report from the German Hodgkin Study Group (GHSG). Blood. 2008;111:71-6.

31. Van der Kaay MAE, Heutte N, Le Stang N, et al for the EORTC Lymphoma Group and GELA. Gonadal function in males after chemotherapy for early stage Hodgkin's lymphoma treated in four subsequent EORTC trials. J Clin Oncol. 2007;25:2825-32.

32. Fermé C, Eghbali H., Meerwaldt J, et al for the European Organization for Research and Treatment of Cancer Lymphoma Group and the Groupe d'Études des Lymphomes de l'Adulte. Combined Modality Treatment for Early Stages Hodgkin's Lymphoma Based on Prognostic Factors. Results of the EORTC–GELA H8 Trial. N Engl J Med. 2007;357:1916-27.

33. Thomas J, Ferme C, Noordijk EM, et al. Results of the EORTC-GELA H9 randomized trials: the H9F trial (comparing 3 different radiation dose levels) and the H9U trial (comparing 3 chemotherapy schemes) in patients with favorable or unfavorable early stage Hodgkin lymphoma. 7th International Symposium on Hodgkin lymphoma Cologne, 2007. Haematol. 2007;92(suppl 5):27.

34. Diehl V, Brillant C, Engert A, et al. HD10: Investigating reduction of combined modality treatment intensity in early stage Hodgkin's lymphoma. Interim analysis of a randomized trial of the German Hodgkin Study Group (GHSG). J Clin Oncol. 2005;23:S561.

35. Noordijk EM, Carde P, Dupouy N, et al. Combined-modality therapy for clinical stage I or II Hodgkin's lymphoma: long-term results of the European Organisation for Research and Treatment of Cancer H7 randomized controlled trials. J Clin Oncol. 2006; 24:3128-35.

36. Specht L, Raemaekers J. Do we need an early unfavorable (intermediate) stage of Hodgkin's lymphoma. Hemat Oncol Clin N Am. 2007;21:881-96.

37. Aleman BMP, Raemaekers JMM, Tirelli U, et al on behalf of the European Organisation for Research and Treatment of Cancer (EORTC) Lymphoma Group. Involved-field radiotherapy for advanced Hodgkin's lymphoma. N Engl J Med. 2003;348:2396-407.

38. Aleman BM, Raemaekers JM, Tomsic R, et al for the EORTC Lymphoma Group. Involved-field radiotherapy for patients in partial remission after chemotherapy for advanced Hodgkin's lymphoma. Int J Radiat Oncol Biol Phys. 2007;67:19-30.

39. Federico M, Luminari S, Dell'Olio M, et al. ABVD vs. COPPEBVCAD (CEC) vs BEACOPP for the initial treatment of patients with advanced Hodgkin's lymphoma (HL). Preliminary results of HD2000 GISL Trial. 7th International Symposium on Hodgkin Lymphoma, 2007. Haematologica. 2007;92(suppl 5):34 (abstract C026).

40. Hasenclever D, Diehl V. A prognostic score for advanced Hodgkin's disease: international prognostic factors project on advanced Hodgkin's disease. N Engl J Med. 1998;339:1506-14.

41. Horning SJ. Risk, cure and complications in advanced Hodgkin disease. Education Book ASH Hematology, 2007:197-203.

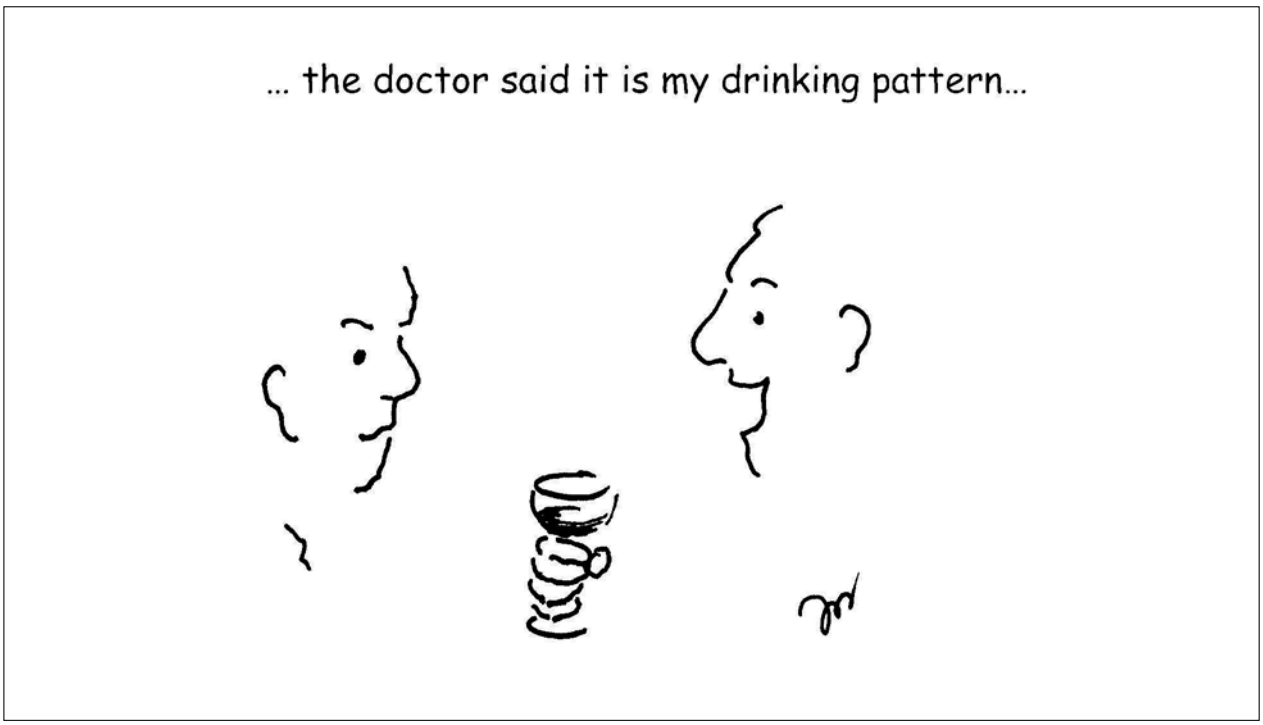
42. Evens AM, Cilley J, Ortiz T, et al. G-CSF is not necessary to maintain over 99% dose-intensity with ABVD in the treatment of Hodgkin lymphoma: low toxicity and excellent outcomes in a 10-year analysis. Br J Haematol. 2007;137:545-52.

43. Raemaekers J, Kluin-Nelemans H, Teodorovic I, et al on behalf of the EORTC Lymphoma Group. The achievements of the EORTC Lymphoma Group. Eur J Cancer. 2002;38:S107-13.

44. Carde P, Koscielny S, Franklin J, et al. Early response to chemotherapy: a surrogate for final outcome of Hodgkin's disease patients that should influence initial treatment length and intensity? Ann Oncol. 2002;13:86-91.

45. Gallamini A, Hutchings M, Rigacci L, et al. Early interim [18F]fluoro-2-deoxy-d-glucose positron emision tomography is prognostically superior to international prognostic score in advanced-stage Hodgkin's lymphoma: a report from a joint Italian-Danish study. J Clin Oncol. 2007;25:3746-52.

46. Van der Maazen RW, Raemaekers JM. Chemotherapy and radiotherapy in Hodgkin's lymphoma: joining in or splitting up? Curr Opin Oncol. 2006;18:660-6.



Raemaekers, et al. Hodgkin's lymphoma: news from an old disease.