Hodgkin's lymphoma in adults

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Management of Hodgkin's lymphoma continues to develop. Outcomes for patients with favourable-risk, early-stage disease are excellent, and serial reductions in intensity of treatment have been made to retain the excellent prognosis while reducing the late effects of treatment. Prognosis is also very good in advanced-stage disease but the rate of relapse is higher than in early-stage disease, and the optimum first-line treatment is unclear. Workers are investigating the role of functional imaging to assess whether treatment can be tailored according to response, with the most intensive therapies reserved for patients predicted to have poor outcomes. In this Seminar we critically appraise the management of Hodgkin's lymphoma in early-stage disease, advanced-stage disease, and at relapse, with a focus on late effects of treatment.

Introduction

Most patients with Hodgkin's lymphoma are cured with first-line therapy. The main challenges are to reduce the toxic effects of treatment while maintaining excellent outcomes, and to improve survival for patients with poor-risk, refractory, or relapsed disease. Since our previous Seminar,[1] there have been important advances in the management of Hodgkin's lymphoma, most notably in the use of PET, deintensification of treatment in selected patients, and the management of relapsed disease.

Epidemiology

Incidence of Hodgkin's lymphoma in the UK and USA is 2·7–2·8 per 100 000 per year, with roughly 1700 new cases diagnosed in the UK every year.[2,3] The disease is more frequent in men than in women, and peaks in incidence are noted in young adults and in people older than 60 years.[4,5] Incidence has remained mostly unchanged during the past two decades.[6,7] Hodgkin's lymphoma is classified as either classical or nodular lymphocyte-predominant.[8] Four subtypes of classical Hodgkin's lymphoma exist, which differ in presentation, sites of involvement, epidemiology, and association with Epstein-Barr virus (table 1); management, however, is broadly similar in all subtypes.[8] Nodular lymphocyte-predominant Hodgkin's lymphoma has a distinct histological appearance, immunophenotype, and clinical course. Understanding of the pathophysiology of Hodgkin's lymphoma continues to develop.[9–11]

Search strategy and selection criteria

We systematically searched Medline and PubMed for articles published between January, 2000 and July, 2012 for the term "Hodgkin's lymphoma" and the related terms "early stage", "advanced stage", and "relapsed" or "refractory". We did not restrict references by language of publication, and relevant references published before the search period were also included. References from relevant articles were also searched. Conference reports and abstracts are included when relevant.

Diagnosis and staging

Hodgkin's lymphoma typically presents as painless lymphadenopathy, which is frequently cervical or supraclavicular. More than 50% of patients have a mediastinal mass, which can be asymptomatic or can present as dyspnoea, cough, or obstruction of the superior vena cava.[12] Systemic symptoms are reported in 25% of patients. Fever, drenching night sweats, and loss of more than 10% of bodyweight over 6 months are termed B symptoms and have prognostic importance. Other symptoms such as pruritis, fatigue, and alcohol-related pain do not have prognostic importance and are thus not regarded as B symptoms. Diagnosis of Hodgkin's lymphoma should be confirmed histologically. Contrast-enhanced CT of the neck, chest, abdomen, and pelvis should be done for staging. Functional imaging with ^{18}F-fluorodeoxyglucose (^{18}F-FDG) PET is increasingly used to stage disease accurately, delineate margins of radiotherapy, and provide a baseline for subsequent response assessment.

Bone-marrow involvement is identified in 5–8% of patients with Hodgkin's lymphoma, but in apparently early-stage disease the rate of involvement is less than 1% and is generally judged too low to justify taking of a bone marrow biopsy.[13–15] In advanced disease, discovery of bone-marrow involvement will not change treatment, but will affect the restaging procedures done at the end of treatment. ^{18}F-FDG PET is sensitive for focal bone-marrow infiltration,[16] and its increasing use will reduce the number of staging trephine biopsies done. Staging of Hodgkin's lymphoma is based on modifications of the Ann Arbor system (panel 1), and is useful for prognostication and treatment planning.

Prognosis and risk stratification

The outlook for patients with early-stage disease (stage I–IIA) is excellent, with overall survival exceeding 90% in many trials. In advanced-stage disease, overall survival is 75–90%. In both early-stage and advanced-stage disease, further stratification according to risk factors is often done. Early-stage disease is stratified into favourable and unfavourable (sometimes referred to as intermediate stage) by some groups according to the presence or absence of risk factors. The definition of early-stage

unfavourable disease varies (table 2), but the most consistently used determinants are disease bulk and the presence of B symptoms. In the UK and the USA, subdivision of early-stage disease is not common practice; instead patients with B symptoms are judged to have advanced disease. However, evidence shows that profound treatment reductions can be made in favourable early-stage disease,[17] and thus identification of this group of patients should be mandatory.

For advanced stage disease, the international prognostic score (also known as the Hasenclever score) is used to predict prognosis.[18] The score is calculated according to seven clinical and laboratory factors (panel 2); the presence of each factor reduces 5 year overall survival on average by 8% (table 3). Risk stratification according to response assessment by interim ^{18}F-FDG PET in both early-stage and advanced-stage disease will probably supplement or replace present methods of assigning risk.

PET in Hodgkin's lymphoma

^{18}F-FDG PET can be used in combination with CT for staging, end-of-treatment and interim assessments, and follow-up surveillance, although its precise role has not been defined. In prospective studies, ^{18}F-FDG PET at diagnosis upstaged 13–24% more patients than did CT.[19–21] When upstaging moves a patient from early-stage to advanced-stage disease (as happened in 7–15% of patients), a change in management is warranted.[19–21] There is no evidence that this change in management affects long-term survival, however, partly because of the success of salvage therapy. Staging ^{18}F-FDG PET also provides a baseline scan against which subsequent scans can be compared.[22]

End-of-treatment ^{18}F-FDG PET can be used to distinguish between fibrotic tissue and residual active disease. In a prospective study,[23] negative end-of-treatment ^{18}F-FDG PET had a 96% (95% CI 91–97) negative predictive value for progression or early relapse in advanced-stage disease. Thus, in advanced-stage patients with a residual mass but a negative end-of-treatment ^{18}F-FDG PET scan, radiotherapy could potentially be omitted. ^{18}F-FDG PET has been adopted in the revised response criteria for lymphoma, which require a negative scan to classify a patient as in complete remission and allows residual masses as long as they are not ^{18}F-FDG avid—so-called metabolic complete remission.[22] Although the negative predictive value of ^{18}F-FDG PET is very high, the positive predictive value is less reliable, with false-positives occurring because of infection, inflammation, increased uptake of ^{18}F-FDG in brown fat, and reactive changes after treatment. Thus, to ascertain whether relapse has occurred, histological evidence is preferable to ^{18}F-FDG PET alone.[24]

The greatest interest is in the potential use of ^{18}F-FDG PET for interim assessment after initial cycles of chemotherapy, with the aim of identification of which patients are cured and which need escalation of treatment. Response after two cycles of chemotherapy is more predictive of outcome than traditional risk stratification based on results of clinical and laboratory tests.[25–27] Data suggest that interim assessment can be even more predictive if done after the first cycle of chemotherapy.[28] Results of prospective clinical trials assessing the escalation or de-escalation of treatment on the basis of interim ^{18}F-FDG PET are awaited. Until conclusive results are available, treatment decisions should not be made by interim assessment. Surveillance ^{18}F-FDG PET has been assessed in routine follow-up, but data do not support such an approach.[29]

There are several unresolved questions relating to the reproducibility and quality control of ^{18}F-FDG PET and the standardised interpretation of minimum uptake. Quantification of ^{18}F-FDG uptake can be assessed as a standard uptake value or by visual assessment. For the purposes of clinical trials, a five-point scale (Deauville scale) that compares the standard uptake value of a lesion with that of the mediastinum or liver is recommended (panel 3).[30]

	EBV association	Epidemiology	Clinical features
Nodular lymphocyte-predominant Hodgkin's lymphoma	No association	Accounts for 5% of all Hodgkin's lymphoma; more common in male than in female patients	75% of patients are early stage; risk of transformation to high-grade non-Hodgkin lymphoma
Classical Hodgkin's lymphoma			
Nodular sclerosis classical Hodgkin's lymphoma	Intermediate association; 10–40% of patients EBV positive	Accounts for 70% of classical Hodgkin's lymphoma in Europe and North America	Mediastinal mass present in 80% of patients; prognosis better than in other subtypes of classical disease
Mixed-cellularity classical Hodgkin's lymphoma	Strong association; up to 75% of patients EBV positive	Accounts for 25% of classical disease; prevalent in patients with HIV infection and developing countries	Peripheral and abdominal lymphadenopathy common; splenic infiltration in 30% of patients
Lymphocyte-rich classical Hodgkin's lymphoma	Intermediate association	Accounts for 5% of classical Hodgkin's lymphoma	Peripheral lymphadenopathy common; mediastinal mass rare
Lymphocyte-depleted classical Hodgkin's lymphoma	Strong association; up to 75% of patients EBV positive	Rarest subtype, accounts for <1% of cases in Europe and North America; prevalent in patients with HIV infection and developing countries	Patients frequently present with advanced-stage disease

EBV=Epstein-Barr virus.

Table 1: **Subtypes of Hodgkin's lymphoma, association with Epstein-Barr virus, epidemiology, and clinical features[8]**

Management

Early-stage favourable disease

Combined modality therapy (chemotherapy and radiotherapy) has replaced radiotherapy alone in localised Hodgkin's lymphoma because it substantially reduces relapse rate through the chemotherapeutic eradication of occult disease outside the radiation field and allows for smaller radiation fields.[31–34] A meta-analysis[35] confirmed a reduction in relapse rate with combined modality therapy, and although it did not report a survival benefit, a separate retrospective study[36] identified mantle field radiotherapy alone as an independent risk factor for death.

The gold-standard treatment for favourable early-stage disease was thought to be four cycles of ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) followed by 36 Gy involved-field radiotherapy (IFRT),[37] but this approach now represents over-treatment. The European Organisation for Research and Treatment of Cancer (EORTC) H9 trial[38] suggested that the radiation dose could be reduced to 20 Gy in patients who achieved complete remission or complete remission unconfirmed after chemotherapy. The German Hodgkin Lymphoma Study Group (GHSG) HD10 trial[17] randomly assigned patients with favourable early-stage disease to two or four cycles of ABVD chemotherapy followed by either 20 Gy or 30 Gy IFRT. At 5 year follow-up, investigators reported no significant difference in freedom from treatment failure or overall survival between the study groups, and more toxic effects in the groups that received four cycles of chemotherapy or 30 Gy IFRT, or both. Two cycles of ABVD and 20 Gy IFRT should therefore be regarded as the standard of care in favourable early-stage disease as defined by the GHSG (ie, <three sites of disease without bulk, extranodal extension, or raised ESR; table 2), with an event-free survival of 91% and an overall survival of 93% at 5 years.

Trials investigating whether radiotherapy can be omitted have also been done,[38–40] and a Cochrane review[41] reported that combined modality therapy was associated with improvements in both progression-free survival (hazard ratio [HR] 0·41, 95% CI 0·25–0·66) and overall survival (0·40, 0·27–0·59), although a more recent investigation[42] that used outmoded, extensive radiotherapy fields suggested that ABVD alone was superior in the long term to sub-total nodal irradiation with or without ABVD. Concerns about the late effects of radiotherapy (especially the increased risk of secondary malignancies) have led some groups to recommend chemotherapy alone in carefully selected patients with early-stage disease when the risk of secondary malignancies is deemed high. Such patients might include women younger than 35 years or those who have a family history of breast cancer for whom the radiation field would incorporate breast tissue.[43,44] Trials[45,46] in early-stage disease (some of which are expected to report in 2013) are assessing whether interim ^{18}F-FDG PET can be used to identify patients who do not need radiotherapy.

Attempts have also been made to reduce the intensity of chemotherapy cycles. The GHSG HD13 trial[47] compared four different variations of ABVD combined with 30 Gy IFRT to establish whether bleomycin and dacarbazine can be omitted. More relapses were reported when either dacarbazine or both dacarbazine and bleomycin were omitted than in patients who received standard treatment, leading to early closure of these groups. The final analysis will investigate the omission of bleomycin, which would

***Panel 1:* Ann Arbor staging system and Cotswold modifications for Hodgkin's lymphoma**

Stage

I Involvement of one lymph-node region or lymphoid structure
II Involvement of two or more lymph-node regions on the same side of the diaphragm
III Involvement of lymph nodes on both sides of the diaphragm
  1 Splenic hilar, coeliac, or portal nodes
  2 Para-aortic, iliac, or mesenteric nodes
IV Involvement of extranodal sites other than one contiguous or proximal extranodal site

Modifying features

A No symptoms
B Presence of fever, drenching night sweats, loss of more than 10% of bodyweight over 6 months
X Bulky disease (mediastinal mass larger than a third of thoracic diameter, or any nodal mass >10 cm in diameter)
E Involvement of one contiguous or proximal extranodal site

	Risk factors	Stratification
GHSG (Germany)	≥3 nodal areas involved, mediastinal bulk*, ESR ≥50 or ESR ≥30 if B symptoms present†, extranodal disease	Favourable=stage I–II with no risk factors; unfavourable (intermediate)=stage I–IIA with ≥1 risk factor, or stage IIB with no mediastinal bulk or extranodal disease
EORTC‡	Age ≥50,mediastinal bulk, ESR ≥50 or ESR ≥30 if B symptoms present, ≥4 nodal sites	Favourable=stage I–II supradiaphragmatic disease with no adverse factors; unfavourable=stage I–II supradiaphragmatic disease with ≥1 risk factor
GELA (France)	Any increase in ESR, age ≥45 years, extranodal disease, haemoglobin ≤105 g/L, lymphocyte count ≤0·6×10^9/L, male sex	Favourable=stage I–II with no risk factors; unfavourable=stage I–IIA with ≥1 risk factor
ECOG/NCI (USA)	Bulky disease§, B symptoms	Early stage=no adverse factors; advanced stage=≥1 risk factor
NCRI (UK)	Bulky disease§, B symptoms	Early stage=no adverse factors; advanced stage=≥1 risk factor

The country in which the research group is based is shown in parentheses. GHSG=German Hodgkin Study Group. EORTC=European Organisation for Research and Treatment of Cancer. GELA=Groupe d'Etudes des Lymphomes de l'Adulte. ECOG=Eastern Cooperative Oncology Group. NCI=National Cancer Institute. NCRI=National Cancer Research Institute. *Mediastinal bulk is defined as a mediastinal mass with a diameter greater than 0·35 times the maximum thoracic diameter. †B Symptoms are unexplained fever, night sweats, or documented unexplained weight loss (>10% bodyweight over 6 months). ‡EORTC early-stage favourable trials do not include very favourable patients—ie, patients with stage IA disease, patients younger than 40 years, or female patients with nodular sclerosing histology. §Bulky disease includes mediastinal mass larger than 0·35 times the transthoracic diameter, and other sites of disease measuring 10 cm or larger.

***Table 2:* Risk stratification of early-stage Hodgkin's lymphoma, by research group**

be advantageous in view of the drug's association with pulmonary fibrosis.

Early-stage unfavourable disease

Combined modality therapy is the standard treatment for unfavourable early-stage disease in most of Europe, although most patients with B symptoms or bulky disease in the UK have been treated with protocols used for advanced disease. In the EORTC H8 trial,[32] IFRT was as effective as extended-field radiotherapy (EFRT) in early unfavourable disease and no difference in outcome was reported between four and six cycles of MOPP–ABV (mechlorethamine, vincristine, procarbazine, prednisolone, doxorubicin, bleomycin, and vinblastine).[32] The GHSG HD8 trial showed that after four cycles of alternating COPP (cyclophosphamide, vincristine, procarbazine, and prednisolone) and ABVD, relapse rate or survival did not differ between the IFRT (30 Gy and an additional 10 Gy to sites of bulk) and EFRT (30 Gy and an additional 10 Gy to sites of bulk) groups, although acute toxic effects were significantly higher in the latter.[48] Although these protocols resulted in high rates of complete remission, relapse rates of up to 15–20% have led to searches for more effective initial chemotherapy.[49]

The EORTC H9 trial[50] randomly assigned patients with early unfavourable disease to four cycles of ABVD, six cycles of ABVD, or four cycles of baseline BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisolone) followed by 30 Gy IFRT in all groups. Investigators noted more toxic effects in patients in the BEACOPP group than in the ABVD groups, but outcome did not differ. The GHSG HD11 trial[49] randomised patients to get four cycles of either ABVD or baseline BEACOPP and either 20 Gy or 30 Gy IFRT. The outcome was inferior after ABVD and 20 Gy radiotherapy, but other treatment groups had similar outcomes, indicating that baseline BEACOPP and 20 Gy IFRT is as effective as ABVD and 30 Gy IFRT. However, because more toxic effects were associated with BEACOPP than with ABVD, most clinicians have concluded that four cycles of ABVD followed by 30 Gy IFRT should remain standard practice. To investigate further whether intensive chemotherapy can improve outcome in this group, the GHSG HD14 trial[51] randomly assigned patients to receive either four cycles of ABVD or two cycles of escalated BEACOPP, followed by two cycles of ABVD with 30 Gy IFRT in both treatment groups. A small but significant improvement in freedom from treatment failure was identified in patients who received escalated BEACOPP and two cycles of ABVD compared with those who received six cycles of ABVD (94·8% *vs* 87·7%, p<0·001), but grade 3 and 4 toxic effects also increased. Therefore, these results do not mandate a change in practice.

Management of advanced disease

The standard treatment for advanced-stage disease is combination chemotherapy. ABVD has better outcomes than do previous regimens such as MOPP (mechlorethamine, vincristine, procarbazine, and prednisolone) and was equivalent to alternation of MOPP and ABVD or a MOPP–ABV hybrid,[52,53] or alternation of ChlVPP (chlorambucil, vinblastine, procarbazine, and prednisolone) with PABLOE (prednisolone, doxorubicin, bleomycin, vincristine, and etoposide).[54] ABVD is associated with lower rates of pulmonary and haematological toxic effects, secondary myelodysplasia, leukaemia, and infertility than is MOPP–ABV, making it a better treatment. ABVD therefore became standard therapy, with rates of progression-free survival of about 70% and overall survival of 82–90%.[53–57] Attempts have been made to improve upon these results. The Stanford V regimen—a weekly regimen of seven drugs given over 3 months combined with extensive radiotherapy—was initially thought to lead to improved outcome. However, findings from a prospective trial[55] comparing this regimen with six to eight cycles of ABVD in the UK showed no difference in outcome. Results of an Italian trial[58] showed that the Stanford V regimen was inferior to ABVD.

In the GHSG HD9 trial,[59,60] patients were randomly assigned to eight cycles of alternating COPP and ABVD, eight cycles of baseline BEACOPP, or eight cycles of escalated BEACOPP, with IFRT delivered to sites of initial bulk and residual masses after chemotherapy in all groups. 10 year freedom from treatment failure was 82% and overall survival was 86% in the escalated BEACOPP group, both of which were significantly better than were results associated with either baseline BEACOPP or COPP and ABVD (although perhaps ABVD would have been a better

Panel 2: **International prognostic index (Hasenclever score) for advanced-stage Hodgkin's lymphoma[17]**

- Age >45 years
- Male sex
- Serum albumin concentration <40 g/L
- Haemoglobin concentration <105 g/L
- Stage IV disease
- Leucocytosis (≥15×10⁹ white cells per L)
- Lymphopenia (<0·6×10⁹ lymphocytes per L, or <8% total white-cell count)

	5 year FFP (SE)	5 year OS (SE)
Score 0	84% (4)	89% (2)
Score 1	77% (3)	90% (2)
Score 2	67% (2)	81% (2)
Score 3	60% (3)	78% (3)
Score 4	51% (4)	61% (4)
Score ≥5	42% (5)	56% (5)

FFP= freedom from progression. OS=overall survival.

Table 3: **Reductions in 5 year freedom from progression and overall survival relative to score on international prognostic index**

***Panel 3:* Deauville criteria for interim ^{18}F-fluorodeoxyglucose PET[29]**

1 No uptake
2 Uptake ≤mediastinum
3 Uptake >mediastinum but ≤liver*
4 Uptake moderately increased at any site compared with the liver
5 Uptake substantially increased at any site compared with the liver, or any new sites of disease

*Score 3 could be judged positive in trials investigating a reduction in therapy, or negative in trials investigating intensification of treatment.

standard comparator than COPP alternated with ABVD). Escalated BEACOPP results in increased haematological toxic effects, infections, secondary malignancies, and rates of infertility compared with both BEACOPP and alternating COPP–ABVD,[60,61] but the improvement in overall survival at 10 years is impressive (overall survival at 10 years was 75% with COPP–ABVD, 80% with baseline BEACOPP, and 86% with esclated BEACOPP).

The GHSG HD12 trial[62] assessed whether the toxic effects of BEACOPP can be reduced; four cycles of escalated BEACOPP were followed by four cycles of baseline BEACOPP and preliminary results suggest that this regimen is not associated with a significant loss in efficacy. Meanwhile the GHSG HD15 trial[63] reported better results and fewer toxic effects and secondary malignancies with six cycles of escalated BEACOPP followed by PET-guided radiotherapy than with either eight cycles of escalated BEACOPP or eight cycles of BEACOPP-14.

Findings from a small Italian trial[56] confirmed that event-free survival was better with escalated BEACOPP than with ABVD. However, salvage was inferior in patients who did not respond to BEACOPP, and thus the overall survival benefit at 7 years was not significant (89% with BEACOPP *vs* 84% with ABVD). The power of this trial was low, but a Cochrane analysis[64] of four trials of escalated BEACOPP (including the Italian study) showed that although progression-free survival increases significantly with escalated BEACOPP (HR 0·53, 95% CI 0·44–0·64), this improvement does not translate to a significant benefit in overall survival (0·8, 0·59–1·09). Some centres previously reserved escalated BEACOPP for patients with high international prognostic scores,[65] but long-term follow-up of the GHSG HD9 trial suggests that the regimen has an equivalent benefit in patients of any score.[60]

The role of radiotherapy in advanced-stage disease is unclear. IFRT to sites of initial disease bulk was previously given to all patients after chemotherapy, and findings from a retrospective analysis[66] of data from the UK suggested that this strategy improved progression-free and overall survival. An EORTC trial[67] randomly assigned patients in complete remission after MOPP–ABV to IFRT or no radiotherapy, and showed no significant differences in event-free or overall survival between the two groups.[67] In the same study, patients in partial remission after chemotherapy benefited from consolidation radiotherapy, leading the investigators to recommend consolidation IFRT only to such patients.[68] However, the findings of the GHSG HD15 trial showed that radiotherapy can be omitted for patients with residual masses if they are PET negative after BEACOPP chemotherapy.[23] Thus, the proportion of patients benefiting from consolidation radiotherapy is probably small.

Randomised trials have established that consolidation of first complete remission with high-dose therapy and autologous stem-cell transplantation has no benefit in progression-free or overall survival, even in patients with high-risk disease.[69–71] Thus, this approach is not recommended.

Response-adapted therapy

Interim ^{18}F-FDG PET in advanced-stage disease has high sensitivity and specificity,[72] and is better than the international prognostic score in prediction of outcome.[25–27] Treatment can be tailored according to the results of interim PET scans in advanced disease. Avigdor and colleagues[65] gave 45 patients two cycles of escalated BEACOPP and then did a PET–CT scan. 72% of patients had a negative scan, and de-escalation to ABVD for a subsequent four cycles led to 4 year progression-free survival of 87%. The GHSG HD18 trial[73] is testing whether the number of cycles of escalated BEACOPP can be reduced from eight to four in patients with a negative interim scan. An alternative approach is to start treatment with ABVD and escalate to BEACOPP if the interim scan is positive.[74,75] This strategy is being prospectively explored in the UK National Cancer Research Institute Response Adapted Therapy using FDG-PET Imaging in Advanced Hodgkin Lymphoma (RATHL) trial.[76] This trial is also assessing the randomised omission of further bleomycin in patients with a negative ^{18}F-FDG PET scan after two cycles of ABVD.

Relapsed or refractory disease and salvage chemotherapy

Roughly 10% of patients with early-stage disease and 20–30% with advanced disease will be refractory to, or relapse after, initial treatment. The strategy for management of relapsed or refractory disease is to deliver salvage chemotherapy, followed by high-dose chemotherapy and autologous stem-cell transplantation in responding patients.[77,78] The outlook of patients with relapsed disease depends on time to relapse, stage at time of relapse, and performance status. Patients with refractory disease—including those who relapse less than 3 months after completion of treatment—have significantly worse outcomes than do those who relapse having previously been in remission.[79] In large German retrospective studies, 5 year overall survival for primary

refractory patients was 26%,[80] compared with 46% for those relapsing 3–12 months after chemotherapy and 71% for those relapsing more than 1 year after treatment.[81]

No trials have directly compared salvage regimens or investigated the optimum number of cycles. Salvage chemotherapy should ideally introduce drugs that were not used in the original treatment, should be reasonably non-toxic, and should not impair subsequent harvest of haemopoietic stem cells.[79] ESHAP (etoposide, methylprednisolone, cytarabine, and cisplatin), DHAP (dexamethasone, cytarabine, and cisplatin), IVE (ifosphamide, etoposide, and epirubicin), and ICE (ifosphamide, carboplatin, and etoposide) are the most widely used, with response rates of 60–80%.[79] BEACOPP has also been successfully used in this setting.[82] Radiotherapy alone could have a role in selected patients with localised late relapse, but the criteria for this situation are hard to define.[83]

For patients not responding to first-line salvage chemotherapy, an alternative salvage regimen such as mini-BEAM (carmustine, etoposide, cytarabine, and melphalan) can be effective as a bridge to transplantation in many patients. The new drug brentuximab vedotin could be useful in this context. A UK prospective trial[84] is investigating the role of allogeneic haemopoietic stem-cell transplantation in the primary refractory setting.

Stem-cell transplantation

Autologous stem-cell transplantation

Data from randomised trials[77,78] show improved progression-free survival with salvage chemotherapy followed by autologous stem-cell transplantation compared with salvage chemotherapy alone. Refinements in techniques, including use of peripheral-blood stem cells and growth factors and improved patient selection and supportive care, have led to a reduction in transplantation-related mortality to less than 3%. The depth of response (ie, complete response *vs* partial response) to salvage chemotherapy before autologous stem-cell transplantation is important, with improved progression-free and overall survival for patients in complete remission,[85] and evidence shows that a negative ^{18}F-FDG PET scan after salvage chemotherapy predicts outcome after autologous stem-cell transplantation.[86] Overall survival in patients with relapsed disease treated with this technique is greater than 65%, compared with 30% in refractory disease.[87]

Use of sequential high-dose therapy to increase the intensity of conditioning before autologous stem-cell transplantation has no obvious benefit compared with the standard BEAM (carmustine, etoposide, cytarabine, and melphalan) regimen and autologous stem-cell transplantation, and is associated with increased toxic effects.[88] Similarly, intensification with tandem autologous stem-cell transplantation has been investigated and could have a role in patients with adverse risk factors, although any potential benefit should be weighed against the increased toxic effects.[89]

Allogeneic haemopoietic stem-cell transplantation

Evidence of a graft-versus-disease effect in Hodgkin's lymphoma[90] has resulted in increased use of reduced-intensity conditioning allogeneic transplantation in patients who did not respond to standard salvage therapy; treatment-related mortality of this procedure in expert centres is roughly 20%.[91,92] Use of donor lymphocyte infusions to harness the graft-versus-disease effect and treat relapse after transplantation has also been shown.[91] In a donor versus no-donor analysis of patients who relapsed after autologous stem-cell transplantation, both progression-free (39·3% *vs* 14·2%) and overall survival (66% *vs* 42%) were significantly higher in the donor group than in the no-donor group ($p<0·001$).[93] Allogeneic transplantation might also be beneficial in selected high-risk patients who have not had autologous stem-cell transplantation, but precise indications are controversial.

New drugs

For patients who relapse after or are unsuitable for allogeneic haemopoietic stem-cell transplantation, treatment is either palliative or experimental. Single-drug chemotherapy with gemcitabine or vinblastine has been used in this setting, with gemcitabine providing an overall response rate of 39% with a median duration of response of 6 months.[94] Although Hodgkin and Reed–Sternberg cells are not usually CD20 positive, responses to rituximab used either alone or in combination with chemotherapy in relapsed disease have been reported.[95] Rituximab in combination with chemotherapy in the first-line setting is being assessed in a GHSG trial (clinicaltrials.gov registration number NCT00515554).

Remarkable response rates in relapsed or refractory disease have been achieved in early phase trials with brentuximab vedotin, an anti-CD30 antibody conjugated to an antimicrotubule drug. In a phase 1 trial of heavily pretreated patients with a median of three previous lines of treatment, the overall response rate was 86% (the rate of complete remission was 25%).[96] Impressive rates of control were also noted in a multicentre phase 2 trial of patients with a median of four lines of previous therapy who relapsed after autologous stem-cell transplantation. The initial results—published in abstract form, with short median follow-up—show an overall response rate of 75% and complete remission in 34% of patients.[97,98] This drug thus shows great promise for disease control in patients with refractory disease or multiple relapses as a bridge to transplantation, and might have a role in earlier stages of the disease.

Other drugs that have shown activity in early-phase trials in relapsed disease include the immunomodulatory agent lenalidomide,[99] the mammalian target of rapamycin inhibitor everolimus,[100] and the pandeacetylase inhibitor panobinostat.[101] Bortezomib (a proteasome inhibitor) has poor activity when used alone, but could have a role in combination with other drugs.[102]

Nodular lymphocyte-predominant Hodgkin's lymphoma

Nodular lymphocyte-predominant Hodgkin's lymphoma accounts for 5% of all Hodgkin's lymphoma diagnoses and is distinguished from classical disease by the absence of Hodgkin and Reed–Sternberg cells and the presence of characteristic lymphocyte-predominant cells, which are sometimes called popcorn cells.[8] Lymphocyte-predominant cells are clonal B cells that have retained the B-cell phenotype and are classically CD30 negative.[8] Most patients (70%) are male and median age at presentation is 30–40 years. Early-stage disease is identified in 75% of patients.[103] Nodular lymphocyte-predominant Hodgkin's lymphoma has an excellent prognosis, but late relapses are frequently recorded.[104] Transformation to diffuse large B-cell lymphoma is reported in 8–14% of patients 4–8 years after diagnosis,[104–106] and the risk of transformation increases with time.[105]

Because of the rarity of nodular lymphocyte-predominant Hodgkin's lymphoma, few prospective trial data are available, and the best treatment is unknown. In view of the excellent long-term survival and young age at presentation, the late effects of treatment should be carefully considered. For patients who have had an excision biopsy taken and have no evidence of residual disease, some clinicians have previously used observation alone, but this strategy could be unacceptable because of the high rate of relapse.[106,107] Early-stage disease can be treated with radiotherapy alone, leading to 10 year progression-free survival of 89% and overall survival of 96%; the rate of relapse is higher in stage 2 than in stage 1 disease, but overall survival does not differ.[108] IFRT is as effective as more extensive radiotherapy and has lower rates of late complications. In advanced disease, combination chemotherapy is needed, but little evidence is available to support a particular regimen. ABVD is often used, but regimens with fewer toxic effects such as CVP (cyclophosphamide, vincristine, and prednisolone) are recommended by some groups.[43] Rituximab has been used as a single agent in phase 2 trials in both front-line and relapsed settings, with response rates of up to 100% but frequent relapses.[109,110] The incorporation of rituximab into chemotherapy regimens might be reasonable, and rituximab maintenance might also be beneficial, although this practice is not proven.

Special situations

Elderly

Elderly patients have poorer survival than do younger patients because of comorbidities, toxic effects of treatment, and reduced treatment intensity. In the absence of comorbidities precluding anthracycline use, standard treatment is recommended in patients younger than 70 years. For elderly patients or those with noteworthy comorbidities, ABVD is thought to be too toxic, and alternative regimens such as VEPEMB (vinblastine, cyclophosphamide, procarbazine, prednisolone, etoposide, mitoxantrone, and bleomycin) are used.[111,112] New drugs with few toxic effects will probably have a role in the treatment of elderly patients with Hodgkin's lymphoma.

Pregnancy

Hodgkin's lymphoma is one of the most common cancers reported in pregnancy.[113] To avoid radiation exposure, staging should be with ultrasonography or whole-body MRI.[114] Radiotherapy should generally be avoided because of the risk of teratogenicity. On the basis of data from small case series, treatment with ABVD seems to be safe, especially in the second and third trimesters.[115] Other treatment options include observation or symptom control with steroids or vinblastine alone until delivery. However, the potential increased risk of relapse or refractory disease with this approach should be considered.

HIV/AIDS

In the era of highly active antiretroviral therapy, the management and disease-specific prognosis of patients with coexisting HIV/AIDS and Hodgkin's lymphoma are the same as for patients with Hodgkin's lymphoma without HIV/AIDS.[116,117]

Late effects of treatment and survivorship

The late effects of treatment are key determinants of the long-term morbidity, mortality, and quality of life of patients treated for Hodgkin's lymphoma and necessitates long-term follow-up. In the first 10 years after treatment most deaths are due to relapse, but after this time deaths due to late effects predominate.[118] Secondary malignancies can be solid organ (most commonly lung, skin, breast, and gastrointestinal) or haematological (leukaemia, myelodysplasia, and secondary lymphomas).[119] Risk of secondary malignancies is highest after treatment in childhood.[120,121] Radiotherapy is associated with increased cancer risk at most irradiated sites, whereas after chemotherapy secondary malignancies are restricted to acute leukaemia, non-Hodgkin lymphoma, and lung cancer.[122] Initial treatment with radiotherapy alone has the highest risk of secondary malignancies because of treatment failures and exposure to subsequent salvage therapy.[123,124] The risk of development of malignant disease in people treated for Hodgkin's lymphoma before adulthood has been estimated to be 18·5 times greater than the general population, with a 30 year cumulative risk of 18% for male patients and 26% for female patients.[121]

The most common secondary malignancy in female patients is breast cancer. Age of younger than 20 years at time of treatment and EFRT incorporating the mediastinum are the most important risk factors.[124,125] The risk of breast cancer was estimated to be 29% (95% CI 20·2–40·1%) in patients who received 40 Gy mediastinal irradiation before age 25 years in one study.[126] UK guidelines recommend that female patients given

supradiaphragmatic radiotherapy are offered screening with yearly mammography or MRI from 8 years after treatment or at age 25 years (whichever is later).[127] US guidelines recommend yearly screening from 10 years after treatment or at 40 years of age (whichever is earlier).[43]

Chemotherapy drugs, especially alkylating agents, contribute to secondary malignancy risk; however, the increase in risk associated with ABVD seems negligible. Small increases in the incidence of myelodysplasia and acute myeloid leukaemia were reported in the BEACOPP groups of the GHSG HD9 trial, although the overall rate of secondary malignant disease was not increased compared with other chemotherapy regimens.[60]

Increases in incidence (noted from 1 to more than 25 years after therapy) of myocardial infarction, congestive cardiac failure, asymptomatic coronary disease, valvular dysfunction, and stroke have all been recorded after treatment for Hodgkin's lymphoma, and the risk of cardiac mortality persists for many years after treatment.[128] The risk is related to supradiaphragmatic radiotherapy, anthracycline-containing chemotherapy, and possibly the use of vinca alkaloids. Traditional cardiovascular risk factors are additive and adjustment of modifiable risk factors is important.

Other late effects include subfertility, endocrine dysfunction, peripheral neuropathy, and local effects from radiotherapy. Fertility is an important consideration in view of the young age of many people diagnosed with Hodgkin's lymphoma. Rates of amenorrhoea are higher, whereas recovery of antimüllerian hormone concentrations and birth rates are lower, in women given BEACOPP than in those given ABVD; being older than 30 years at time of treatment was an important risk factor for subfertility.[129] In one study,[130] 50% of women given escalated BEACOPP did not recover normal menstruation compared with less than 5% after ABVD. Attempts to protect female fertility during BEACOPP treatment by hormonal manipulation have been unsuccessful.[131] Pregnancy is frequently possible after autologous stem-cell transplantation if menstruation was normal before high-dose therapy. In men, the rate of azoospermia after treatment with BEACOPP is 87–93%, whereas ABVD induces permanent azoosepermia in less than 5% of patients.[61,132,133] For male patients, sperm storage can usually be offered before treatment, whereas fertility-sparing measures in female patients are time consuming and, because of treatment delays, not always advisable.

Conclusion

Today most patients with Hodgkin's lymphoma are cured and current developments are likely to lead to further, if small, improvements in overall survival because of both improved tumour eradication and reduction of late effects. Because of the success of the treatment of Hodgkin's lymphoma, proof of further advances will require very large trials with long-term follow-up, and international collaboration will be essential.

Contributors

Both authors contributed equally to the writing of this Seminar.

Conflicts of interest

DL has served on advisory boards for Roche and Millennium Pharmaceuticals, and has received travel grants from Roche and Chugai. WT declares that he has no conflicts of interest.

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