Part II: Hodgkin's lymphoma—diagnosis and treatment

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The outcome of patients with all stages of Hodgkin's lymphoma has improved dramatically over the past few decades. This is mainly due to the use of risk-adapted therapies using intensive polychemotherapeutic regimens in combination with other modalities. Patients with early favourable or unfavourable (intermediate) stage disease receive two or four cycles of chemotherapy, respectively, followed by involved-field radiotherapy (20–30 Gy). Advanced stage Hodgkin's lymphoma is treated more aggressively using six to eight cycles of chemotherapy but the effectiveness of consolidative radiotherapy for patients who show a complete response after chemotherapy alone is still unknown. The main challenge in the near future will be the development of strategies that decrease late morbidity and mortality but retain the same efficacy of current regimens. In this paper we review current diagnostic techniques and management strategies used to treat Hodgkin's lymphoma, and the range of new modalities being used to improve long-term outcome and patient quality of life.

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The management of Hodgkin's lymphoma (figure 1) has undergone a paradigm shift over the past few years with the use of combined chemotherapy and involved-field radiation in early-stage disease and effective drug regimens capable of inducing high remissions in advanced disease (figure 2). Moreover, the introduction of effective salvage high-dose chemotherapy with peripheral stem-cell transplantation for relapsed disease, a better understanding of prognostic factors, and a more sensitive realisation of the magnitude of late treatment morbidity and mortality has further improved management of the disease.

Diagnosis and staging

An excisional biopsy of a suspicious lymph node should be done for the initial diagnosis of Hodgkin's lymphoma. The extent of disease is assessed with the four-stage Cotswolds modification of the Ann Arbor classification.[1] Information about prognostic factors such as mediastinal mass, other bulky nodal disease, and the extent of subdiaphragmatic disease is included in this classification (table 1).

Two-thirds of patients with newly diagnosed Hodgkin's lymphoma have radiographical evidence of intrathoracic involvement. A large mediastinal mass has been arbitrarily defined as a ratio greater than a third between the largest transverse diameter of the mediastinal mass and the transverse diameter of the thorax.[1]

PET is used in some instances to improve staging at initial diagnosis. PET may also be used in patients with residual tumour masses to discriminate between active lymphoma and fibronecrotic tissue. Several, mostly monocentric, studies were done showing that PET has a negative predictive value ranging from 85% to 100%, which indicates that patients with a negative PET result will not suffer from a relapse in most instances. By contrast, the positive predictive value of PET for residual lesions after completion of therapy is not validated for routine clinical use because it varies by about 60%, indicating that in some instances only half of patients with positive PET images will experience treatment failure in the future. Therefore, the exact role of PET for patients with residual lesions after treatment for Hodgkin's lymphoma has yet to be determined.[2–4]

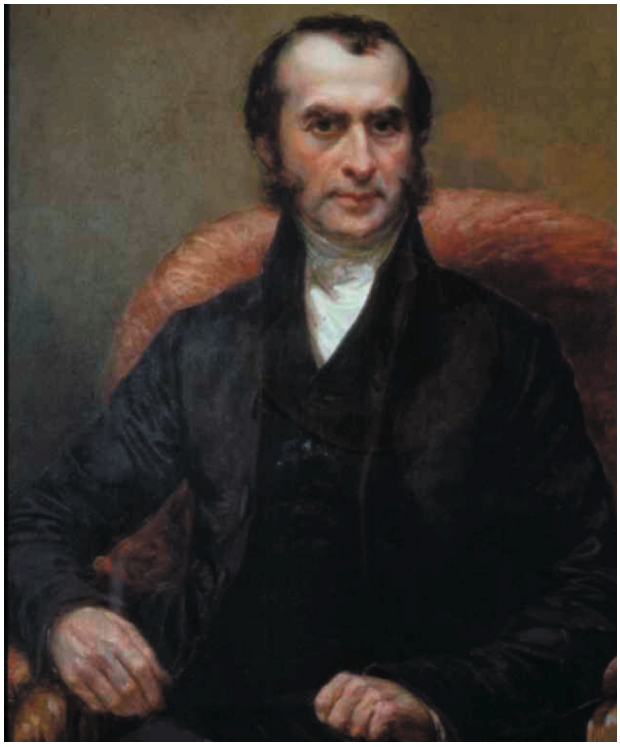

Figure 1. Thomas Hodgkin, 1798–1866.

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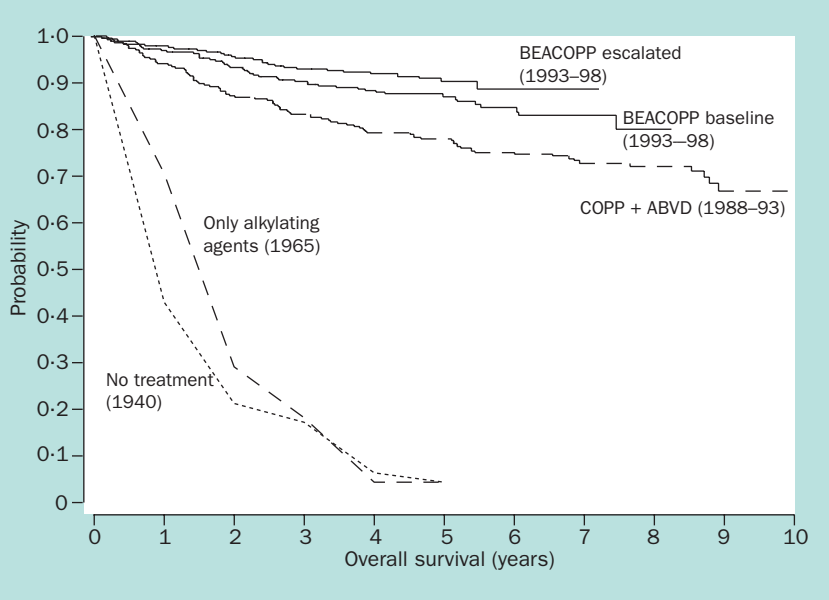

Figure 2. Progress made in the treatment of advanced-stage Hodgkin's lymphoma during the past 40 years. BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone; COPP, cyclophosphamide, vincristine, procarbazine, and prednisone; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine.

Choice of treatment

Prognostic factors and treatment groups

Despite an enormous effort to define clinically relevant and generally acceptable prognostic factors, stage and systemic B-cell symptoms are still the two major determinants for stratifying patients with Hodgkin's lymphoma. Bulky disease (>10 cm) has recently emerged as a third prognostic factor that meets general acceptance. In the USA, most centres treat patients according to the traditional classifications of early stages (I–IIA or B) and advanced stages (III–IVA or B; I–IIB with bulky disease). Further prognostic factors are often used to assign stage I–II patients to a more unfavourable group. In Europe, the European Organization for Research and Treatment of Cancer (EORTC) and the German Hodgkin's Lymphoma Study Group (GHSG) have defined stage I–II patients as unfavourable or intermediate if any of the adverse factors listed in table 2 are present.

Prognostic factors for advanced-stage disease

The International Prognostic Score (IPS)[5] was developed to identify patients with advanced-stage disease either for treatment intensification or for treatment reduction (table 3). Several study groups are currently tailoring treatment strategies at first diagnosis depending on the risk for treatment failure (IPS 0–2 and 3–7), but stratification of patients on the basis of the IPS score is still an experimental approach. By contrast, the three-level scheme of division of Hodgkin's lymphoma into early favourable, early unfavourable (intermediate), and advanced-stage disease is a robust instrument to tailor risk-adapted therapy.

Early-stage Hodgkin's lymphoma

Early-stage favourable disease

Until recently, early-stage favourable Hodgkin's lymphoma was treated with extended-field irradiation without chemotherapy. However, due to the high incidence of relapse (about 25–30%) and fatal long-term effects (secondary neoplasms or cardiac toxicity), extended-field radiotherapy is now being abandoned by most study groups in favour of combined therapy[6,7] consisting of a short-duration chemotherapy (eg, two cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine; ABVD) and involved-field irradiation (20–30 Gy). An improvement in overall survival is unlikely to show in future study generations because of already excellent long-term results obtained with combined modality treatment (ie, a 10-year overall survival of about 95%). Thus, many of the ongoing and recently completed studies were developed in an attempt to reduce the long-term

Table 1. Cotswolds staging classification

Stage	Description
Stage I	Involvement of a single lymph-node region or lymphoid structure (eg, spleen, thymus, Waldeyer's ring) or involvement of a single extralymphatic site
Stage II	Involvement of two or more lymph-node regions on the same side of the diaphragm (hilar nodes, when involved on both sides, constitute stage II disease); localised contiguous involvement of only one extranodal organ or site and lymph-node region(s) on the same side of the diaphragm (IIE). The number of anatomic regions involved should be indicated by a subscript (eg, II_3)
Stage III	Involvement of lymph-node regions on both sides of the diaphragm (III), which may also be accompanied by involvement of the spleen (III_S) or by localised contiguous involvement of only one extranodal organ site (IIIE) or both (IIISE)
III1	With or without involvement of splenic, hilar, celiac, or portal nodes
III2	With involvement of para-aortic, iliac, and mesenteric nodes
Stage IV	Diffuse or disseminated involvement of one or more extranodal organs or tissues, with or without associated lymph-node involvement
Designations applicable to any disease stage	
A	No symptoms
B	Fever (temperature >38°C), drenching night sweats, unexplained loss of more than 10% of body weight within the previous 6 months
X	Bulky disease (a widening of the mediastinum by more than one third of the presence of a nodal mass with a maximal dimension greater than 10 cm)
E	Involvement of a single extranodal site that is contiguous or proximal to the known nodal site

Table 2. Definition of treatment groups according to the EORTC and GHSG

	EORTC	GHSG
Risk factors	A large mediastinal mass	A large mediastinal mass
	B age ≥50 years	B extranodal disease
	C elevated ESR*	C elevated ESR*
	D ≥4 involved regions	D ≥3 involved regions
Early-stage favourable	CS I-II without risk factors (Supradiaphragmatic)	CS I-II without risk factors
Early-stage unfavourable (intermediate)	CS I-II with ⩾1 risk factors (Supradiaphragmatic)	CS I, CSIIA with ⩾1 risk factors CS IIB with C/D but without A/B
Advanced Stage	CS III-IV	CS IIB with A/B CS III-IV

GHSG, German Hodgkin's Lymphoma Study Group; EORTC, European Organization for Research and Treatment of Cancer. *Erythrocyte sedimentation rate (≥50 without B symptoms or ≥30 with B symptoms).

complications of treatment without increasing mortality from Hodgkin's lymphoma. In these trials, intensity of irradiation and chemotherapy is varied and radiation is even omitted within some controlled studies.

Treatment recommendations

Fortunately, death from Hodgkin's lymphoma in patients with early-stage disease with a favourable prognosis is rare and, therefore, overall survival is not a useful parameter to evaluate mid-term results. Current trials should be judged by freedom from first recurrence rates, acute, and long-term morbidity and mortality, and by novel criteria such as quality-of-life and cost effectiveness. In summary, radiotherapy alone is no longer the treatment of choice in most centres in Europe and the USA. Combinations of chemotherapy and involved-field radiotherapy is the most common treatment strategy; 2–4 cycles of ABVD are considered the international gold standard for early-stage Hodgkin's lymphoma in combination with 20–30 Gy involved-field radiotherapy. Whether chemotherapy alone is sufficient to control disease, has yet to be determined.

Early-stage unfavourable disease

It is generally accepted that patients with early-stage unfavourable (intermediate) Hodgkin's lymphoma qualify for combined modality therapy. However, the prognostic effect of a single risk factor and the optimum chemotherapy and radiation regimens are topics for debate.

In contrast to favourable prognosis stage I–II disease, less toxic and less intense chemotherapy regimens (eg, epirubicin, bleomycin, vinblastine, and prednisone, EBVP) have not been shown to be as effective as ABVD or combinations containing ABVD. Therefore, ABVD has become the standard regimen for unfavourable stage I–II disease (with risk factors), but 5% of patients progress during therapy and 15% relapse early, many of whom seem to be resistant to salvage therapy. This evidence led to the development of novel more intense regimens (eg, BEACOPP or Stanford V), which are being evaluated in ongoing studies in combination with involved-field radiotherapy (20–30 Gy).

The effectiveness of involved-field radiation with extended-field radiation has been shown recently along with evidence that involved-field radiation is sufficient to control occult disease when combined with chemotherapy.[6,8] Acute and long-term toxic effects are a major issue in patients with stage I–II disease and involved-field radiation shows equivalent results but has less toxicity compared with extended field radiotherapy. Whether radiotherapy is necessary at all in unfavourable patients is currently being determined in a trial by the National Cancer Institute of Canada; patients with unfavourable stage I–II disease are randomly assigned to receive combined modality therapy (two cycles ABVD and extended-field irradiation) or chemotherapy alone (four to six cycles of ABVD).

Treatment recommendations

The outcome of treatment for patients with unfavourable prognosis stage I–II Hodgkin's lymphoma has improved dramatically over the past three decades mainly because of the use of chemotherapy. Four cycles of effective chemotherapy (eg, ABVD) followed by 20–30 Gy involved-field radiotherapy is the new standard for patients with early unfavourable Hodgkin's lymphoma. Whether four to six cycles of chemotherapy without irradiation are sufficient has still to be determined.

Advanced-stage Hodgkin's lymphoma

The pioneers: MOPP and ABVD

A few decades ago, patients with advanced stages of Hodgkin's lymphoma were incurable. De Vita and colleagues at the National Cancer Institute achieved a 50% cure rate in patients with advanced-stage disease with a drug combination called MOPP (mechlorethamine, vincristine, procarbazine, and prednisone).[9–11] The same regimen with chlorambucil or cyclophosphamide in place of mechlorethamine showed similar efficacy and was associated with less acute toxicity. The British National Lymphoma Investigation (BNLI) compared MOPP with the same regimen but with lomustine in place of

Table 3. Final cox regression model of the International Prognostic Score

Factor	Log hazard ratio	Relative risk	p value
Serum albumin <4g/dL	0·40+0·10	1·49	<0·001
Haemoglobin <10·5 g/dL	0·30+0·11	1·35	0·006
Male	0·30+0·09	1·35	0·001
Stage IV disease	0·23+0·09	1·26	0·011
Age ≥45 years	0·33+0·10	1·39	0·001
White-cell count ≥15 000/mm³	0·34+0·11	1·41	0·001
Lymphocyte count <600/mm³ or <8% of white-cell count	0·31+0·10	1·38	0·002

mechlorethamine in a randomised trial and found no significant differences.[12]

The efforts to improve the efficacy and reduce the toxicity of the original MOPP regimen did not result in higher cure rates, but possibly achieved less acute gastrointestinal and neurological toxic effects.

Despite the great accomplishments with MOPP and MOPP-like regimens, 15–30% of patients did not reach complete remission and only about 50% of the patients could be cured, leading to the introduction of the ABVD regimen.[13] A pivotal trial of patients with advanced Hodgkin's lymphoma compared MOPP, ABVD, and alternating MOPP/ABVD without additive radiotherapy and showed equal therapeutic results for ABVD and MOPP/ABVD (progression-free survival and overall survival). A long-term follow-up of this study over 15 years has recently been published showing 45–50% progression-free survival and 65% overall survival for ABVD and MOPP/ABVD.[14] Other large multicentre trials tested the efficacy of hybrid regimens and showed that the MOPP/ABV hybrid was equally effective as alternating MOPP/ABVD, but more effective than sequential MOPP and ABVD.[15,16] One main advantage of ABVD is the relatively low incidence of long-term toxic effects compared with alkylating-agent-based regimens. MOPP, for example, induces infertility in almost all men[17] and in women over 30 years of age.[18] Moreover, patients treated with MOPP and radiotherapy have a 3% lifetime risk of developing acute leukaemia.[19] By contrast, ABVD has the advantage of fewer acute toxic effects, particularly sterility and secondary leukaemias or myelodysplastic syndromes. Nevertheless, there are cardiotoxicity and pulmonary side-effects with six to eight courses of ABVD, which are even more common with the addition of radiotherapy. ABVD is the accepted standard chemotherapy used in combined modality regimens against which all experimental drug combinations should be tested in the future.[20]

Dose-intensified chemotherapy regimens

In the early 1990s, clinical trials addressing dose-intensity were initiated. Most of the trials introduced etoposide as a novel chemotherapeutic agent and used higher doses than in ABVD.

Stanford V is a seven-drug regimen (mechlorethamine, doxorubicin, vinblastine, vincristine, bleomycin, etoposide, prednisone, and granulocyte colony-stimulating factor)[21] that was given weekly for a total of 12 weeks in combination with consolidative radiotherapy to sites of initial bulky disease. In a phase II single-centre trial of 142 patients[22] the 5-year freedom from progression was 89% and the overall survival was 96% at a median of 5·4 years. Few mid-term toxic effects were reported and fertility could be preserved in both men and women.

Similarly, the Manchester group developed the abbreviated, 11-week chemotherapy regimen vincristine, doxorubicin, prednisolone, etoposide, cyclophosphamide, and bleomycin (VAPEC-B) and compared it with chorambucil, vinblastine, procarbazine, prednisolone, etoposide, vincristine, and doxorubicin (ChlVPP/EVA) with radiotherapy for previous bulky disease or residual disease (n=282).[23,24] After a median follow-up of 4·9 years freedom from progression, event-free survival, and overall survival were significantly better with ChlVPP/EVA than with VAPEC-B.

In 1992, the GHSG did a series of comprehensive phase II and III trials of patients with advanced Hodgkin's lymphoma to find out whether increasing dose density could improve the outcome of patients with advanced disease. The BEACOPP regimen was devised on the basis of the COPP/ABVD regimen—without vinblastine and dacarbazine but with the addition of etoposide. Baseline BEACOPP included equivalent doses, but was given in a 22-day cycle rather than a 29-day cycle, and this standard combination was also given with escalating doses.[25] After a series of pilot studies, the GHSG designed the HD9 trial, comparing COPP/ABVD, baseline BEACOPP, and increasing doses of BEACOPP in patients with advanced Hodgkin's lymphoma.[26] About two-thirds of patients received consolidative radiotherapy. The freedom from treatment failure rate was 87% for escalated BEACOPP, 76% for baseline BEACOPP, and 69% for COPP/ABVD at 5 years. A major difference was also observed in the rate of primary progressive disease during initial therapy, which was significantly lower with escalated BEACOPP (2%), baseline BEACOPP (8%), or COPP/ABVD (12%, $p<0·001$). The

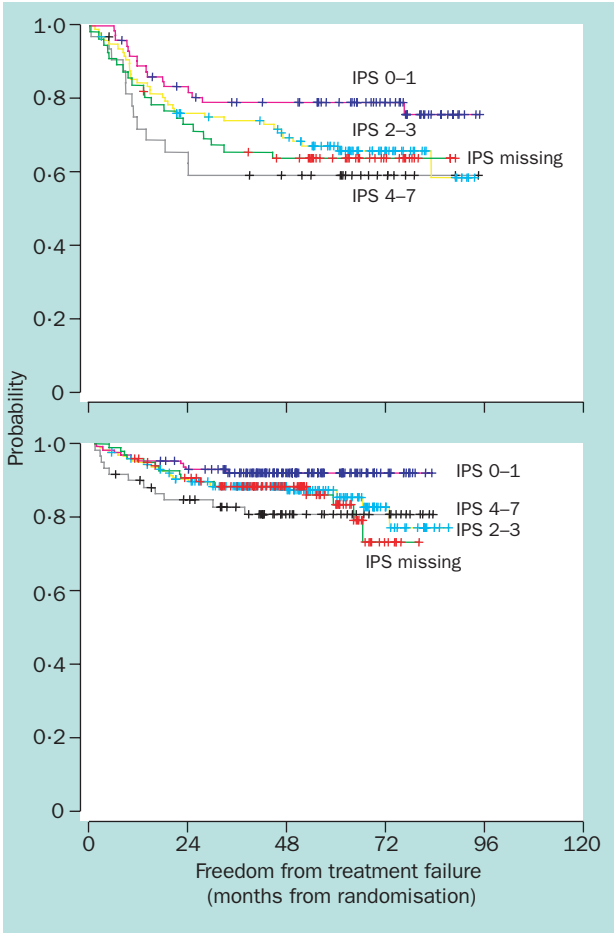

Figure 3. Kaplan-Meier analysis showing overall survival for patients with advanced-stage Hodgkin's lymphoma, according to the International Prognostic Score (IPS), treated with four cycles of COPP/ABVD (a) or eight cycles of escalated BEACOPP (b).

overall survival rates were 83% for COPP/ABVD, 88% for baseline BEACOPP, and 91% for escalated BEACOPP; the survival difference between COPP/ABVD and escalated BEACOPP was significant (p<0·002).

When the IPS is applied to patients with advanced-stage Hodgkin's lymphoma, the superiority of the escalated BEACOPP regimen over COPP/ABVD is shown for all risk groups. It is most pronounced in patients with poor prognosis (IPS 4–7) with a significant difference in overall survival of 15% (82% and respectively 67%; figure 3). On the basis of these results, the GHSG decided to give increased doses of BEACOPP to patients with low-risk disease.

Hodgkin's lymphoma is becoming a highly curable disease and treatment-associated toxic effects—particularly fertility and quality of life—are becoming increasingly important issues especially in younger patients (panel). About 80% of men treated with escalated BEACOPP will suffer from sterility at the end of chemotherapy, whereas patients treated with ABVD will have no lifelong problems with fertility. Nevertheless, modern techniques in reproductive medicine mean that most male patients can be offered the chance to father healthy children, and most young men agree to cryopreservation of their sperm before start of therapy.

BEACOPP is also associated with a higher rate of haematological toxic effects. Furthermore, there is a higher occurrence of acute myeloid leukaemia (AML) and myelodysplastic syndrome (MDA): escalated BEACOPP, 9 cases of AML/MDS reported; BEACOPP baseline, 4 cases of AML/MDS reported; and COPP/ABVD, 1 case of AML/MDS reported. However, the total rate of secondary neoplasia, including the development of other lymphomas, was highest in patients treated with COPP/ABVD. The death rate at 5 years, including all acute and late causes of deaths, was 18·8% for COPP/ABVD, 13% for baseline BEACOPP, and 8·5% for escalated BEACOPP. So at a median follow-up of 5 years, ten more patients out of 100 treated with COPP/ABVD had died. This evidence highlights the importance of overall survival as the ultimate denominator for determining the benefit of a treatment strategy for advanced Hodgkin's lymphoma.

Role of radiotherapy

An important issue in the treatment of advanced Hodgkin's lymphoma is the added efficacy and late toxicity of adjuvant radiotherapy after anthracycline-containing chemotherapy. In a recently published EORTC trial,[27] patients who had showed complete responses after six to eight cycles of MOPP/ABV were randomly assigned to receive involved-field radiation or no further treatment. An analysis of the 739 patients showed that involved-field irradiation did not improve relapse-free survival or overall survival in patients who already achieved a complete response with MOPP/ABV. Remarkably, those who had a partial response and were treated with additional radiotherapy, had an overall 5-year survival rate of about 85–90%, which is comparable to patients who showed complete remission after chemotherapy alone.

From that study it is concluded, that only patients with a partial remission after effective chemotherapy may benefit from involved-field radiotherapy, whereas patients who show complete remission after chemotherapy alone do not benefit from consolidative radiotherapy. This finding has large implications for the treatment of advanced disease because many treatment-associated long-term toxic effects can be attributed to radiotherapy. Although techniques and strategies have changed during the past few decades, it has not been shown whether reduced doses, field sizes, and improved ionisation sources are less harmful in combination with polychemotherapy. Overall, the risk of developing a secondary cancer (mostly solid tumours) after radiation for Hodgkin's lymphoma is 25% after 25 years and there is still no limit in the incidence of secondary tumours.[28] Moreover, there exists a dose-risk association for the development of radiation-induced tumours for breast cancer and this risk increases linearly from 4 Gy to 40 Gy.[29] Interestingly, a risk reduction for breast cancer was shown when chemotherapy was added to radiotherapy which is possibly associated with menopausal age, suggesting that tumorigenesis after radiation is promoted by ovarian hormones.

Long-term toxic effects after treatment for Hodgkin's lymphoma

Minor	Endocrine dysfunctions (hypothyroidism, hypo-a-menorrhea, decreased libido)
	Long-term immunosuppression
	Viral Infections (Herpes simplex, Varziella zoster, papillomaviruses, warts viruses)
Serious	Lung fibrosis from radiation plus bleomycin
	Myocardial damage from anthracyclines and radiation
	Sterility in men and women
	Growth abnormalities in children and adolescents
	Opportunistic infections
	Psychological problems
	Psychosocial disturbances
	Fatigue
Potentially fatal	Acute myeloid leukaemia/myelodysplastic syndrome
	Non-Hodgkin lymphomas
	Solid tumours (lung, breast, and colon cancer, sarcomas)
	Overwhelming bacterial sepsis after splenectomy or spleen irradiation (OPSI)

Treatment recommendations

The progress made in clinical research during the past 40 years has highlighted the pertinent question of how extended and intense treatment and long-term side-effects should be balanced against high success rates at the onset of treatment.

ABVD with or without consolidative radiotherapy is widely considered the gold standard for the treatment of advanced Hodgkin's lymphoma. Whether this strategy is justified on the basis of existing data has to be evaluated by each individual doctor. Whether escalated BEACOPP is superior over ABVD is the subject of a recently initiated global study comparing six to eight courses of ABVD with four courses of escalated BEACOPP and four courses of baseline BEACOPP with or without radiation for all risk groups and for high-risk patients only (IPS≥4). Because escalated BEACOPP is significantly superior to COPP/ABVD for primary progression and freedom from treatment failure,

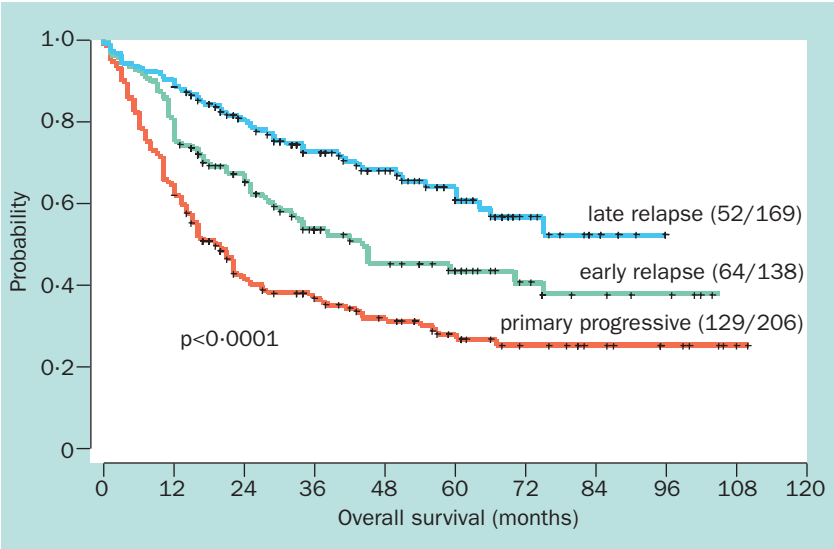

Figure 4. Kaplan-Meier analysis showing overall survival in patients with primary progressive, early and late relapsed Hodgkin's disease after first-line polychemotherapy (German Hodgkin's Lymphoma Study Group; n=513, total=3809).[30,31]

the GHSG recommends escalated BEACOPP in all patients independent of IPS-defined risk factors. This practise results in a 10–20% higher freedom-from-progression rate and an overall survival benefit of about 8% over ABVD or C(M)OPP/ABVD at 5 years. However, there is a higher initial burden of toxic effects and a higher rate of acute myeloid leukaemia and myelodysplastic syndrome and infertiltity with the use of the escalated regimen.

Primary progressive and relapsed Hodgkin's lymphoma

Depending on the initial treatment used, patients with refractory or relapsed disease have various treatment options. Conventional chemotherapy is the treatment of choice for patients who relapse after initial radiotherapy for early-stage disease. The survival of these patients is at least equal to that of patients with advanced-stage disease initially treated with chemotherapy.[30,31] By contrast, the therapeutic options for individuals with relapsed disease after initial chemotherapy include salvage radiotherapy, salvage chemotherapy, and high-dose chemotherapy followed by autologous stem-cell transplant,[32–34] or even allogeneic stem-cell transplant.[35]

Prognostic factors in patients relapsing after primary chemotherapy

It was first noted in 1979 that the length of remission to first-line chemotherapy had a marked effect on the success of subsequent salvage treatment.[36] Thus, failure of chemotherapy can be used to classify disease as primary progressive Hodgkin's lymphoma (patients who never achieved a complete remission), early relapses (within 12 months of complete response), and late relapses (relapse more than 12 months after the end of therapy). Prognosis of patients according to these risk factors is shown in figure 4. In patients with primary progressive disease treated with conventional chemotherapy, virtually no patient survives more than 8 years. By contrast, the projected 20-year survival for patients with early relapse or late relapse was 11% and 22%, respectively.[37]

Treatment of primary progressive and relapsed disease

Patients who relapse after a first complete response can achieve a second complete response with salvage treatment including radiotherapy for localised relapse in previously non-irradiated areas, or conventional chemotherapy. The optimum treatment for recurrence after primary chemotherapy is less clear. High-dose chemotherapy followed by autologous stem-cell transplant has been shown to produce 30–65% long-term disease-free survival in selected patients with refractory and relapsed disease.[33,38–41] The most compelling evidence for the superiority of high-dose chemotherapy and autologous stem-cell transplant in relapsed Hodgkin's disease comes from two reports from the BNLI and the GHSG/European Group for Blood and Marrow Transplantation (EBMT).

In the BNLI trial, patients with relapsed or refractory Hodgkin's lymphoma were treated with conventional-dose mini-BEAM (carmustine, etoposide, cytosine arabinoside, and melphalan) or high-dose BEAM with autologous stem-cell transplant.[42] The actuarial 3-year event-free survival was significantly better in patients who received high-dose chemotherapy (53% *vs* 10%).

The largest randomised, multicentre trial was done by the GHSG/EBMT. Patients who relapsed after chemotherapy were randomly assigned to four cycles of Dexa-BEAM (addition of dexamethasone) or two cycles of Dexa-BEAM followed by BEAM and autologous stem-cell transplant. The final analysis showed freedom from treatment failure in the high-dose chemotherapy group was 55% *vs* 34% for patients receiving an additional two cycles of chemotherapy. Overall survival was not significantly different.[43]

Sequential high-dose chemotherapy

In 1997, a multicentre phase II trial with a high-dose sequential chemotherapy and a final myeloablative course was initiated for patients with relapsed or primary progressive Hodgkin's lymphoma.[44] After two cycles of DHAP (dexamethasone, cytosine arabinoside, cisplatin), patients with partial response or complete response received sequential high-dose chemotherapy consisting of cyclophosphamide, methotrexate plus vincristine, and etoposide followed by BEAM and autologous stem-cell transplant. Freedom-from-treatment-failure rates and overall survival suggest a high efficacy of this regimen in patients with relapsed disease. Thus, the GHSG, EORTC, and EBMT began a prospective randomised study to compare the effectiveness of standard high-dose chemotherapy (BEAM) with a sequential high-dose

chemotherapy after initial cytoreduction with two cycles of DHAP for patients with early or late relapsed disease, and for patients in second relapse who have had no previous high-dose chemotherapy.

Lymphocyte-predominant Hodgkin's lymphoma

Nodular lymphocyte-predominant Hodgkin's lymphoma is a rare subtype with an annual incidence in developed countries of about 0·1–0·3 per 100 000 inhabitants. The clinical manifestation is indolent, with predominantly peripheral lymph nodes. About 75% of the patients have stage IA disease and organ involvement seldom occurs. The disease tends to relapse frequently, even after 10–15 years of remission. Development of secondary non-Hodgkin's lymphoma is not uncommon. However, current treatment strategies should take into account the favourable prognosis and avoid late effects such as cardiac and pulmonary complications, and development of secondary lymphomas.

Caution is indicated when identifying patients who might benefit from a reduction of treatment intensity. First, immunostaining is needed for a reliable differential diagnosis between lymphocyte-predominant Hodgkin's lymphoma, classic Hodgkin's lymphoma, and certain non-Hodgkin's lymphoma variants. Second, patients with advanced-stage lymphocyte-predominant disease (20–25%) show a substantially worse overall survival and tumour-free survival than patients with early-stage lymphocyte-predominant disease which is similar to advanced-stage classic Hodgkin's lymphoma.[45] This evidence implies that thorough staging and eventually aggressive treatment is needed irrespective of histological subtype. The EORTC and the GHSG at present recommend that patients with stage I–IIA disease should be treated with involved-field radiation (30 Gy). Recently, the anti-CD20 antibody, rituximab, was used for treatment of lymphocyte-predominant Hodgkin's lymphoma at first diagnosis or relapse. Remissions were observed in up to 80% of cases, but follow-up is still short and the use of rituximab must be considered experimental.[46,47]

Experimental therapies

Promising experimental therapeutic strategies for patients with Hodgkin's lymphoma are currently not available, unlike the situation for individuals with non-Hodgkins' lymphoma. However, current approaches include passive immunotherapy with antibody-based regimens for specific targeting of malignant cells (eg, anti-CD30 antibodies)[48] as well as active immunotherapy with modulation of the cellular immune response using cytokines, tumour vaccines, or gene transfer. The combination of experimental strategies with chemotherapy are potential future treatments.

Conclusion

The rationale behind treatment of patients with Hodgkin's lymphoma is to classify patients as having early favourable, unfavourable (intermediate), or advanced-stage disease according to anatomic stage and B-symptoms (and possibly prognostic factors, such as the IPS). Patients with early favourable disease should be treated with a moderate chemotherapy (typically two to four cycles of ABVD) and involved-field radiation (20–30 Gy). Patients with early unfavourable disease should receive four cycles of ABVD followed by involved-field radiation (20–30 Gy). Patients with advanced-stage disease should be treated more aggressively with six to eight cycles of chemotherapy. The role of consolidative radiation for patients with advanced-stage disease who showed complete remission after chemotherapy has been questioned recently. Patients who show complete responses after six to eight courses of anthracyclin-containing chemotherapy seem not to benefit from consolidative radiation but for patients with partial responses, consolidative radiation is beneficial. For patients with progressive or relapsing disease, depending on previous treatment, therapeutic options include radiotherapy, chemotherapy, and high-dose chemotherapy followed by autologous stem-cell transplantation, which has been shown to be superior to standard chemotherapy in two clinical trials. In summary, Hodgkin's lymphoma has become a highly curable disease over the past few decades because of the introduction of effective polychemotherapy and the use of risk-adapted radiotherapy using reductions in dose and field size. For doctors treating newly diagnosed patients it is imperative that early complete remission is achieved with the most effective treatment strategy and the least long-term toxic side-effects.

Search strategy and selection criteria

We identified relevant articles with searches of PubMed with the terms "Hodgkin's disease", "Hodgkin's lymphoma", "chemotherapy", "radiotherapy", "prognostic factors". References from relevant articles were also included. Additional papers were selected from the authors personal collections.

Conflicts of interest

None declared.

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References

1 Lister TA, Crowther D, Sutcliffe SB, et al. Report of a committee convened to discuss the evaluation and staging of patients with Hodgkin's disease: Cotswolds meeting. *J Clin Oncol* 1989; **7:** 1630–6 [erratum in *J Clin Oncol* 1990; **8:** 1602].
2 de Wit M, Bohuslavizki KH, Buchert R, et al. 18FDG-PET following treatment as valid predictor for disease-free survival in Hodgkin's lymphoma. *Ann Oncol* 2001; **12:** 29–37.
3 Jerusalem G, Beguin Y, Fassotte MF, et al. Early detection of relapse by whole-body positron emission tomography in the follow-up of patients with Hodgkin's disease. *Ann Oncol* 2003; **14:** 123–30.
4 Weihrauch MR, Re D, Scheidhauer K, et al. Thoracic positron emission tomography using 18F-fluorodeoxyglucose for the evaluation of residual mediastinal Hodgkin disease. *Blood* 2001; **98:** 2930–34.
5 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.
6 Noordijk E, Carde P, Hagenbeek A. Combination of radiotherapy and chemotherapy is advisable in all patients with clinical stage I-II Hodgkin's disease. Six-year results of the EORTC-GPMC controlled clinical trials 'H7-VF,' 'H7-F' and 'H7-U'. *Int J Radiat Oncol Biol Phys* 1997; **39:** 173.
7 Sieber M, Frnaklin J, Tesch H, et al. Two cycles ABVD plus extended field radiotherpay is superior to radiotherpay alone in early stage Hodgkin's disease: Results of the German Hodgkin's Lymphoma study group (GHSH) trial HD7. *Blood* 2002; **100:** 341 (abstr).

8 Engert A, Schiller P, Jostig A, et al. Involved-field radiotherapy is equally effective and less toxic compared with extended-field radiotherapy after four cycles of chemotherpay in patients with early stage unfavourable Hodgkin's lymphoma: results of the HD8 trial of the German Hodgkin's Lymphoma Study Group. *J Clin Oncol* 2003; **21:** 3601–08.
9 DeVita V, Hubbard S. Hodgkin's disease. *N Engl J Med* 1993; **328:** 560–65.
10 Longo DL, Young RC, Wesley M, et al. Twenty years of MOPP therapy for Hodgkin's disease. *J Clin Oncol* 1986; **4:** 1295–306.
11 Bonadonna G, Valagussa P, Santoro A. Alternating non-cross-resistant combination chemotherapy or MOPP in stage IV Hodgkin's disease. A report of 8-year results. *Ann Intern Med* 1986; **104:** 739–46.
12 Hancock B. Randomised study of MOPP (mustine, Oncovin, procarbazine, prednisone) against LOPP (Leukeran substituted for mustine) in advanced Hodgkin's disease. British National Lymphoma Investigation. *Radiother Oncol* 1986; **7:** 215–21.
13 Bonadonna G, Zucali R, Monfardini S, et al. Combination chemotherapy of Hodgkin's disease with adriamycin, bleomycin, vinblastine, and imidazole carboxamide versus MOPP. *Cancer* 1975; **36:** 252–59.
14 Canellos GP, Niedzwiecki D. Long-term follow-up of Hodgkin's disease trial. *N Engl J Med* 2002; **346:** 1417–18.
15 Glick JH, Young ML, Harrington D, et al. MOPP/ABV hybrid chemotherapy for advanced Hodgkin's disease significantly improves failure-free and overall survival: the 8-year results of the intergroup trial. *J Clin Oncol* 1998; **16:** 19–26.
16 Duggan DB, Petroni GR, Johnson JL, et al. A randomized comparison of ABVD and MOPP/ABV hybrid for the treatment of advanced Hodgkin´s disease: report of an intergroup trial. *J Clin Oncol* 2003; **21:** 607–14.
17 Sherins RJ, DeVita VT Jr. Effect of drug treatment for lymphoma on male reproductive capacity. Studies of men in remission after therapy. *Ann Intern Med* 1973; **79:** 216–20.
18 Schilsky RL, Sherins RJ, Hubbard SM, et al. Long-term follow up of ovarian function in women treated with MOPP chemotherapy for Hodgkin's disease. *Am J Med* 1981; **71:** 552–56.
19 Blayney DW, Longo DL, Young RC, et al. Decreasing risk of leukemia with prolonged follow-up after chemotherapy and radiotherapy for Hodgkin's disease. *N Engl J Med* 1987; **316:** 710–14.
20 Diehl V. Advanced Hodgkin's disease: ABVD is better, yet is not good enough! *J Clin Oncol* 2003; **21:** 583–85.
21 Bartlett NL, Rosenberg SA, Hoppe RT, et al. Brief chemotherapy, Stanford V, and adjuvant radiotherapy for bulky or advanced-stage Hodgkin's disease: a preliminary report. *J Clin Oncol* 1995; **13:** 1080–88.
22 Horning SJ, Hoppe RT, Breslin S, et al. Stanford V and radiotherapy for locally extensive and advanced Hodgkin's disease: mature results of a prospective clinical trial. *J Clin Oncol* 2002; **20:** 630–37.
23 Radford JA, Rohatiner AZS, Dunlop DJ. Preliminary results of a four-centre randomised trial paring weekly VAPEC-B chemotherapy with the ChlVPP/EVA hybrid regimen in previously untreated patients. *Proc Am Soc Clin Oncol* 1997; **16:** 12.
24 Radford JA, Rohatiner AZ, Ryder WD, et al. ChlVPP/EVA hybrid versus the weekly VAPEC-B regimen for previously untreated Hodgkin's disease. *J Clin Oncol* 2002; **20:** 2988–94.
25 Diehl V. Dose-escalation study for the treatment of Hodgkin's disease. The German Hodgkin Study Group (GHSG). *Ann Hematol* 1993; **66:** 139–40.
26 Diehl V, Franklin J, Pfreundschuh M, et al. German Hodgkin's Lymphoma Study Group. Standard and increased-dose BEACOPP chemotherapy compared with COPP-ABVD for advanced Hodgkin's disease. *N Engl J Med* 2003; **348:** 2386–95.
27 Aleman BM, Raemaekers JM, Tirelli U, et al; European Organization for Research and Treatment of Cancer Lymphoma Group. Involved-field radiotherapy for advanced Hodgkin's lymphoma. *N Engl J Med* 2003; **348:** 2396–406.
28 van Leeuwen FE, Klokman WJ, Veer MB, et al. Long-term risk of second malignancy in survivors of Hodgkin's disease treated during adolescence or young adulthood. *J Clin Oncol* 2000;**18:** 487–97.
29 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.
30 Josting A, Rueffer U, Franklin J, et al. Prognostic factors and treatment outcome in primary progressive Hodgkin`s lymphoma—a report from the German Hodgkin`s Lymphoma Study Group (GHSG). *Blood* 2000; **96:** 1280–86.
31 Josting A, Franklin J, May M, et al. New prognostic score based on treatment outcome of patients with relapsed Hodgkin's lymphoma registered in the database of the German Hodgkin's lymphoma study group. *J Clin Oncol* 2002; **20:** 221–30.
32 Canellos GP. Treatment of relapsed Hodgkin's disease: strategies and prognostic factors. *Ann Oncol* 1998; **9** (suppl 5)**:** 91–96.
33 Josting A, Katay I, Rueffer U, et al. Favorable outcome of patients with relapsed or refractory Hodgkin's disease treated with high-dose chemotherapy and stem cell rescue at the time of maximal response to conventional salvage therapy (Dex-BEAM). *Ann Oncol* 1998; **9:** 289–95.
34 Brice P, Divine M, Simon D, et al. Feasibility of tandem autologous stem-cell transplantation (ASCT) in induction failure or very unfavorable (UF) relapse from Hodgkin's disease (HD). SFGM/GELA Study Group. *Ann Oncol* 1999; **10:** 1485–88.
35 Khouri IF, Keating M, Korbling M, et al. Transplant-lite: induction of graft-versus-malignancy using fludarabine-based nonablative chemotherapy and allogeneic blood progenitor-cell transplantation as treatment for lymphoid malignancies. *J Clin Oncol* 1998; **16:** 2817–24.
36 Fisher RI, DeVita VT, Hubbard SP, et al. Prolonged disease-free survival in Hodgkin's disease with MOPP reinduction after first relapse. *Ann Intern Med* 1979; **90:** 761–63.
37 Longo DL, Duffey PL, Young RC, et al. Conventional-dose salvage combination chemotherapy in patients relapsing with Hodgkin's disease after combination chemotherapy: the low probability for cure. *J Clin Oncol* 1992; **10:** 210–18.
38 Bierman PJ, Bagin RG, Jagannath S, et al. High dose chemotherapy followed by autologous hematopoietic rescue in Hodgkin's disease: long-term follow-up in 128 patients. *Ann Oncol* 1993; **4:** 767–73.
39 Reece DE, Connors JM, Spinelli JJ, et al. Intensive therapy with cyclophosphamide, carmustine, etoposide +/- cisplatin, and autologous bone marrow transplantation for Hodgkin's disease in first relapse after combination chemotherapy. *Blood* 1994; **83:** 1193–99.
40 Armitage JO, Bierman PJ, Vose JM, et al. Autologous bone marrow transplantation for patients with relapsed Hodgkin's disease. *Am J Med* 1991; **91:** 605–11.
41 Gribben JG, Linch DC, Singer CR, et al. Successful treatment of refractory Hodgkin's disease by high-dose combination chemotherapy and autologous bone marrow transplantation. *Blood* 1989; **73:** 340–44.
42 Linch DC, Winfield D, Goldstone AH, et al. Dose intensification with autologous bone-marrow transplantation in relapsed and resistant Hodgkin's disease: results of a BNLI randomised trial. *Lancet* 1993; **341:** 1051–54.
43 Schmitz N, Pfistner B, Sextro M, et al. German Hodgkin's Lymphoma Study Group. Aggressive conventional chemotherapy compared with high-dose chemotherapy with autologous haemopoietic stem-cell transplantation for relapsed chemosensitive Hodgkin's disease: a randomised trial. *Lancet* 2002; **359:** 2065–71.
44 Josting A, Rudolph C, Mapara M, et al. Cologne high-dose sequential chemotherapy in relapsed and refractory Hodgkin lymphoma—results of a large multicenter study for the prospective randomized HDR-2 trial of the German Hodgkin Lymphoma Study Group (GHSG). *Blood* 2002; **100:** 812 (abstr).
45 Diehl V, Sextro M, Franklin J, et al. Clinical presentation, course, and prognostic factors in lymphocyte-predominant Hodgkin's disease and lymphocyte-rich classical Hodgkin's disease: report from the European Task Force on Lymphoma Project on Lymphocyte-Predominant Hodgkin's Disease. *J Clin Oncol* 1999; **17:** 776–83.
46 Rehwald U, Schulz H, Reiser M, et al. German Hodgkin Lymphoma Study Group (GHSG). Treatment of relapsed CD20+ Hodgkin lymphoma with the monoclonal antibody rituximab is effective and well tolerated: results of a phase 2 trial of the German Hodgkin Lymphoma Study Group. *Blood* 2003; **101:** 420–24.
47 Ekstrand BC, Lucas JB, Horwitz SM, et al. Rituximab in lymphocyte-predominant Hodgkin disease: results of a phase 2 trial. *Blood* 2003; **101:** 4285–89.
48 Borchmann P, Treml JF, Hansen H, et al. The human anti-CD30 antibody 5F11 shows in vitro and in vivo activity against malignant lymphoma. *Blood* 2003: **102:** 3737–42.

Cell-cycle targeted therapies

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Eukaryotic organisms depend on an intricate and evolutionary conserved cell cycle to control cell division. The cell cycle is regulated by a number of important protein families which are common targets for mutational inactivation or overexpression in human tumours. The cyclin D and E families and their cyclin-dependent kinase partners initiate the phosphorylation of the retinoblastoma tumour suppressor protein and subsequent transition through the cell cycle. Cyclin/cdk activity and therefore control of cell division is restrained by two families of cyclin dependent kinase inhibitors. A greater understanding of the cell cycle has led to the development of a number of compounds with the potential to restore control of cell division in human cancers. This review will introduce the protein families that regulate the cell cycle, their aberrations in malignant progression and pharmacological strategies targeting this important process.

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Eukaryotic cell division occurs in four phases of the cell cycle (figure 1). The cell is prepared for DNA replication in G1 phase, then chromosomes are replicated during S phase. A gap period, G2, allows preparation for mitosis, before chromosome segregation and cytokinesis in M phase (mitosis). During development, differentiation, or growth-factor withdrawal, cells can enter an inactive period G0, before returning to G1.

Cell-cycle checkpoints ensure faithful chromosome replication and separation, thereby maintaining genetic stability. Failure of these checkpoints to arrest the cell after appropriate stimuli is a hallmark of cancer.[1] One checkpoint, the restriction point, occurs in mid-G1; after this point, cells become independent of growth factors and commit to cell division.[2] Genetic aberrations of regulators of restriction-point passage occur at high frequency in human tumours.

This review discusses the cyclin/cyclin-dependent kinase (cdk) complex and the cdk inhibitors (CKIs) that coordinate restriction-point passage. The discussion covers phase I and II data on agents that target cyclin/cdk activity, such as flavopiridol, UCN-01, and inhibitors of proteosomes and histone deacetylase.

Cell-cycle controversies and the continuum model

Although majority opinion accepts the restriction point as an important model on which to base the interpretation of current cell-cycle data, challenges have been raised to the concepts of restriction point, G0 phase, and cellular checkpoints, based on criticisms of experimental methods used to synchronise cell cultures. Rather than proposing that cells arrest at the restriction point on withdrawal of growth factor, the continuum model predicts that, although cells are arrested with a G1 phase amount of DNA, they are not arrested at any defined point in the cell cycle. When growth-factor restimulation occurs, cells do not enter S phase synchronously, as might be expected from the restriction-point model, but in a sequence determined by their order before growth-factor withdrawal.[3] For the purposes of this review, however, discussion is based on the widely accepted restriction-point model.

Figure 1. Fluorescent light micrograph of human HeLa cells in M phase of the cell cycle.

Cell-cycle regulators and restriction-point control

Disruption of restriction-point control is a common biological feature in human cancer. Cell-cycle progression is regulated by two protein classes, the cyclins and their kinase partners, the cyclin-dependent kinases (cdks). Restriction-point passsage is coordinated by two families of cyclins, the cyclin D family (D1, D2, and D3) and the cyclin E family (E1 and E2). The D-type cyclins bind to and activate cdks 4 and 6, and cyclins E1 and E2 interact with and activate cdk2. The

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