Clinical aspects of Hodgkin’s disease

Most patients are cured: even those with advanced disease

Hodgkin’s disease is uncommon—1213 cases occurred in England and Wales in 1983, representing 0.7% of malignant tumours (excluding skin cancers). The disease occurs world wide, predominantly in men, and presents most commonly in young adults and in those aged 45-75. The rarity of Hodgkin’s disease and the complexities of its management mean that it is best treated by those with an extensive experience of lymphomas. Comprehensive reviews of the disease are available, but we present here a review for the generalist.

Pathology
The diagnosis of Hodgkin’s disease rests on recognising Reed-Sternberg cells in a cellular background appropriate to one of the subtypes of the disease. Despite the application of many techniques—including cell culture, immunohistochemistry, and studies of gene rearrangement—the histogenesis of the Reed-Sternberg cell remains elusive.

There is an agreed classification for Hodgkin’s disease, but recent immunological and clinical studies have suggested that Hodgkin’s disease with lymphocyte predominance should be split once again into a nodular and a diffuse type. The nodular form is almost certainly a B cell lymphoma, and unlike its diffuse counterpart has a relapsing clinical course. The prognosis for both subtypes is excellent, but second malignancies (particularly large cell lymphomas) may be a feature of this condition.

Nodular sclerosing Hodgkin’s disease, often a disease of young women, remains by far the most common and characteristic form. One group has suggested that nodular sclerosing Hodgkin’s disease may be subdivided on the basis of the number of Reed-Sternberg and Hodgkin’s cells and the degree of lymphocyte depletion. This group has found this grading to be useful prognostically, although other groups have found that the degree of fibrosis is the only factor that has predictive value.

Hodgkin’s disease with mixed cellularity is characteristically a disease of older men and carries a worse prognosis. Hodgkin’s disease with lymphocyte depletion encompasses the previously described categories of diffuse fibrosis and reticular Hodgkin’s disease. Diffuse fibrosis occurs predominantly in elderly men who often present with systemic symptoms but without much lymphadenopathy. Diagnosis is usually from the results of bone marrow trephine, or liver biopsy or at necropsy.

Lymphocyte depleted Hodgkin’s disease of the reticular subtype (Hodgkin’s sarcoma) is often misdiagnosed. Several retrospective studies have shown that many cases diagnosed as reticular Hodgkin’s disease are in fact non-Hodgkin’s lymphomas or other subtypes of Hodgkin’s disease. When such cases are excluded patients with reticular Hodgkin’s disease have a similar survival to patients with disease of other histological types of comparable stage.

Staging the disease
The treatment of Hodgkin’s disease is determined by assessing the extent and bulk of the disease and the degree of systemic disturbance as reflected by the erythrocyte sedimentation rate and B symptoms (unexplained fever above 38°C, weight loss of more than 10%, and night sweats).

All patients should have determined a full blood count, an erythrocyte sedimentation rate, liver and renal function tests, and a chest radiograph. Computed tomograms of the chest provide more information but are not routinely required. A unilateral bone marrow trephine from the posterior iliac crest is necessary only in patients with B symptoms, raised alkaline phosphatase activity, or stage III or IV disease (see table for definitions). Abdominal examination should be supplemented by abdominal ultrasonography and lymphangiography; alternatively, computed tomography provides similar information, although it is probably less sensitive and certainly less convenient for follow up. Other investigations—for example, bone scanning—are not routinely required.

Clinical and radiological examination of the abdomen understages 25-30% of patients with Hodgkin’s disease above the diaphragm—largely because of unrecognised disease in the spleen. In the early era of chemotherapy, when wide field irradiation provided the only cure, doctors routinely evaluated the abdomen by laparotomy to define the stage of the disease. In the past 15 years this policy has been re-evaluated with the advent of effective combination chemotherapy. Although no satisfactory randomised trials have been published, consensus is that the staging laparotomy has had little or no impact on survival. This is largely because salvage combination chemotherapy is so good. Furthermore, it has been shown that the spleen (which used to be removed at the staging laparotomy) may be effectively treated with either radiotherapy or combination chemotherapy. Most groups use laparotomy only in those patients with a good prognosis who have a low or intermediate risk of the spleen being invaded by tumour, but some groups use laparotomy hardly at all.

Ann Arbor staging of Hodgkin’s disease

<table>
<thead>
<tr>
<th>Stage</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Disease in a single region of lymph nodes</td>
</tr>
<tr>
<td>II</td>
<td>Disease in two or more regions of lymph nodes on the same side of the diaphragm</td>
</tr>
<tr>
<td>III</td>
<td>Disease in regions of lymph nodes on both sides of the diaphragm</td>
</tr>
<tr>
<td>IV</td>
<td>Diffuse or disseminated disease in one or more extralymphatic organs or tissues—for example, liver, bone marrow, or bone—with or without disease in lymph nodes</td>
</tr>
</tbody>
</table>

The suffix A is added for patients without symptoms and B for patients with any of drenching night sweats, weight loss of 10% or more, or unexplained fever. Disease in specific sites proved by biopsy is identified by a suffix—for example, M₁ for diseases in the bone marrow. Localised disease beyond the nodes is indicated by adding the letter E.
Prognostic factors

It has been known for several years that advancing stage and B symptoms are associated with an increasingly adverse prognosis.\textsuperscript{21} The classic B symptoms have, however, been re-evaluated, and only unexplained fever and weight loss seem to worsen the prognosis.\textsuperscript{22,23} It has also been suggested that severe pruritus should again be included as a B symptom.\textsuperscript{24} Several clinical series have now shown that increasing age,\textsuperscript{25} being male, an increasing erythrocyte sedimentation rate, and an increasing number of disease sites are associated with a poorer prognosis.\textsuperscript{25,26,27} Other factors that may be important in patients treated with radiotherapy for stage I or II disease are the histological grade of the tumour (although this is true only for nodular sclerosing disease)\textsuperscript{28} and the presence of a mediastinal mass.\textsuperscript{29} For patients treated with chemotherapy the dose and rate of delivery of drugs, whether they achieve an early complete remission, and disease site seem to be important.\textsuperscript{30,31}

Management of Hodgkin’s disease by stage

STAGES I AND IIA

Supradiaphragmatic stage I or IIA disease is a common presentation of Hodgkin’s disease, and the results of treatment are good: 70-85\% of patients with non-bulky disease remain free of relapses after radiotherapy alone.\textsuperscript{32-34} Patients with disease below the diaphragm require a different approach.\textsuperscript{35}

Various treatments are used for patients with small volume mediastinal disease that is clinically staged as IA or IIA. Some units use mantle radiotherapy in low risk patients and treat any relapse with chemotherapy. Other units combine mantle radiotherapy with upper abdominal and splenic irradiation in all patients in an attempt to treat subclinical disease and reduce relapse. Alternatively, chemotherapy or combined modalities may be used for patients at high risk of relapse.

For patients whose small volume mediastinal disease has been pathologically staged as IA or IIA mantle radiotherapy is adequate, particularly for those with good prognostic features.\textsuperscript{36}

Patients with bulky mediastinal disease (occupying more than one third of the transthoracic diameter) generally do poorly if treated with radiotherapy alone: unacceptable damage to normal lung may occur, and relapse within the treatment field is common.\textsuperscript{37,38} Most centres now treat such patients initially with chemotherapy; radiotherapy is given once the mediastinal mass has shrunk.

STAGE IIIA

Most British centres now treat all patients with stage IIIA disease with chemotherapy alone and achieve excellent results.\textsuperscript{39} Initial or supplementary irradiation does not improve prognosis, and over three quarters of patients are cured.\textsuperscript{40}

STAGES IIB, IIE, AND IV

Patients in these advanced stages are best treated by combination chemotherapy. In the United States patients with pathological stage IIB disease are treated by subtotal or total nodal irradiation—with excellent results.\textsuperscript{41} This approach requires, however, a staging laparotomy. Although the published reports are not adequate to prove it, chemotherapy seems a reasonable alternative and is commonly used in Britain.

Over half (56\%) of the patients with stages IIB-IVB disease who were originally treated with MOPP have been continuously free of relapses over 10-20 years of follow up.\textsuperscript{42}

Salvage chemotherapy

Relapse after initial treatment occurs most commonly within three years, but late relapse is well recorded.\textsuperscript{43} Patients relapsing after extended field radiotherapy are generally treated with chemotherapy, and about half will be cured.\textsuperscript{44} Patients with advanced disease who fail to respond to initial combination chemotherapy or who relapse within a year are treated with an alternative drug combination, but their prognosis is often poor.\textsuperscript{45} Relapse after one year is often treated by repeating the original chemotherapy.\textsuperscript{46} Some patients with initial widespread disease will relapse with nodal disease, and salvage has been achieved with radiotherapy in some of such cases.\textsuperscript{47}

Patients with refractory disease or multiple relapses but without bone marrow infiltration may be treated with high dose chemotherapy and autologous bone marrow transplantation.\textsuperscript{48} Initial results have been surprisingly good, and this approach is thus likely to be used earlier in the course of the disease.

Treatment

RADIOThERAPy

Megavoltage irradiation is the initial treatment for localised Hodgkin’s disease. Doses of 3500-4400 cGy to areas of disease and 3000-3500 cGy to adjacent areas are commonly used. Irradiation of the spleen and low dose irradiation of the lungs and liver are possible and are used in high risk patients by some groups.\textsuperscript{1,2,5,19}

Randomised trials comparing limited with more extensive treatment have shown equivalent survival, but those given limited treatment have higher relapse rates and so more often need salvage chemotherapy.\textsuperscript{29} It is now generally accepted that wide field irradiation should be used as initial treatment for most low stage cases. Complex planning and simulation of treatment are required, and the use of a linear accelerator is highly desirable.

CHEMOTHERAPY

Combination chemotherapy with a minimum of six courses is the best treatment for patients with advanced disease. There is no place for initial treatment with a single agent. Delivery of the full treatment on schedule seems to be important in determining the prognosis.\textsuperscript{29,47} A combination of mustine, vincristine, procarbazine, and prednisolone (MOPP) has for two decades been the standard chemotherapy.\textsuperscript{26} In the past 15 years groups have tried to reduce the toxicity of MOPP and increase its efficacy. Various less toxic regimens have been devised in which mustine, vincristine, or both, have been replaced.\textsuperscript{28,48} Published results suggest equivalent cure rates for these regimens, which are now used commonly.

Attempts to increase the efficacy of MOPP have focused on adding further active drugs such as doxorubicin, bleomycin, vinblastine, and dacarbazine in alternating seven and eight drug combinations.\textsuperscript{31,32} Initial studies suggest that such treatment may improve survival if given early on in the disease. Large randomised trials are in progress to confirm or refute this hypothesis.

COMBINED MODALITY TREATMENT

The combined use of chemotherapy and radiotherapy has been used in all stages of the disease.\textsuperscript{49} Remission rates are higher and relapse occurs less frequently. Randomised trials, however, have shown little or no survival benefit from this approach, and second malignancies—predominantly leukaemia—and sterility are more common. Combined treatment is still commonly used in bulky (particularly mediastinal) disease.\textsuperscript{33,34}
Toxicity

Toxicity related to treatment (particularly chemotherapy) has probably been more extensively evaluated for Hodgkin’s disease than for any other neoplasm—because the range of toxicities is wide and patients usually survive long term. Toxicities may be short term and related to treatment or long term—for example, infertility and second malignancies. These topics are extensively reviewed elsewhere; while cure remains the paramount objective attempts to devise less toxic treatments continue.

Conclusions

In few conditions does the right treatment so emphatically alter the course of events as in Hodgkin’s disease. There is, however, no room for complacency. Treatment must be further improved, and toxicity must be reduced. Surprisingly the pathogenesis of this condition remains obscure, and the next important advances in our understanding of treatment of this disease are likely to derive from work in the laboratory rather than in the clinic.

We thank Professor D H Wright for his valuable contribution to the manuscript and Ms Lorraine Spencer for her secretarial help.

G M MEAD
Consultant Medical Oncologist
J M A WHITEHOUSE
Professor of Medical Oncology
Cancer Research Campaign Medical Oncology Unit, Southampton General Hospital, Southampton SO9 4XY