Changing priorities in Hodgkin's disease

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Despite greatly improved survival rates for patients with Hodgkin's disease its management has become complex and continues to evolve. Ten years ago order was brought into the management of Hodgkin's disease by introducing lymphangiography of the legs,¹ staging laparotomies,² extended field radiotherapy using megavoltage equipment,³ and effective combination chemotherapy.⁴ Now, however, there is pressure to abandon "conventional" management based on these principles.

Staging laparotomies² increased our knowledge of the natural history of Hodgkin's disease and allowed the introduction of an effective staging classification.⁵ With this classification groups of patients may be selected for different treatments according to stage.⁶ Arguments against staging laparotomies have been advanced recently. They tend to be based on the fact that new or more "aggressive" treatments have been introduced that are applicable to most patients.⁷ Until such treatments have proved their efficacy, however, staging laparotomies should not be abandoned in patients who clinically have less than stage IIIB or IV disease.

Recently a case for substaging symptom-free patients with disease above and below the diaphragm (IIIA) has been made. Desser *et al*⁸ divided stage III patients into two subgroups (III₁ and III₂) on the basis of surgical staging. Those patients with abdominal disease limited to the "upper" abdominal lymphatic structures and nodes around the coeliac vessels, spleen, and porta hepatis were called III₁. Those with stage III₂ had the lower abdominal lymphatics and the para-aortic, iliac, or mesenteric nodes affected. All their patients received total nodal irradiation with or without combination chemotherapy. The study showed that stage III₂ patients had a dramatically better survival (100% *v* 47%) when combination chemotherapy was added. In the stage III₁ patients chemotherapy did not improve survival.

Rosenberg⁹ has pointed out that these results are difficult to interpret as the survival figures are derived from all stage III₂ patients, both with and without systemic symptoms (stage IIIA or B), and radiotherapy alone has been shown to be inadequate treatment for stage IIIB patients. In addition only two-thirds of the patients in the study were randomly selected. There were only five deaths in the subgroup of 16 III_{2A} patients, and the group was too small to permit any conclusions.

An abstract from Stein *et al*¹⁰ recently reported the results of a collaborative study examining the same question retrospectively. In a group of 135 patients with stage IIIA disease survival and disease-free survival for patients with sub-stage III₁ and III₂ were assessed by type of treatment. Ninety patients received radiotherapy alone and 45 a combination of radiotherapy and chemotherapy. Disease-free survival at five years was considerably better in the radiotherapy and chemotherapy group in both subgroups than in those receiving radiotherapy only. Differences in survival at five years, however, were much less dramatic and only just reached significance in the III₂ patients (III₁ 100% *v* 92%, *p* > 0.20; III₂ 84% *v* 59%, *p* > 0.03).

An analysis from Stanford of the data on 172 patients with stage IIIA disease was presented at the same meeting.¹¹ Eighty-five received total lymphoid irradiation and six cycles of MOPP (mustine, vincristine, procarbazine, and prednisolone), and 87 received total lymphoid irradiation only. Disease-free survival

and survival were assessed for each treatment group when the patients were analysed by substages III₁ and III₂, the extent to which the spleen was affected, total number of sites affected, histology, presence or absence of extranodal disease, and clinical stage assigned to the patient before pathological staging. In the group receiving total lymphoid irradiation alone the only significant prognostic factors for disease-free survival were the extent of splenic disease (*p* = 0.009) and total number of sites affected (*p* = 0.03). The addition of six courses of MOPP to the irradiation significantly improved the overall disease-free survival (63% *v* 86% at 10 years, *p* = 0.002), and this was also true in many subgroups. The addition of chemotherapy did not significantly improve overall survival at 10 years (61% *v* 85% *p* = 0.38); subdivision into III₁ and III₂ produced no significant improvement in survival for those who had chemotherapy, and only those subgroups with extensive splenic disease (*p* = 0.03) or more than four sites of disease (*p* = 0.05) showed improved survival with combined treatment.

Selection of subgroups

Selection of subgroups of patients who will benefit from combined modality treatment can be made only on the basis of prolonged and scrupulously controlled clinical trials. Such trials of adjuvant chemotherapy were started at Stanford¹²⁻¹⁵ over 10 years ago and are only now starting to provide answers. The results soon showed that adding adjuvant MOPP after irradiation significantly improved the disease-free survival of early-stage patients. A more important question is whether such treatment improves survival, chemotherapy being very effective in salvaging patients who have relapsed from their initial radiotherapy-induced remission. In the most recent analysis of the Stanford study¹⁶ 253 patients have been randomly allocated to total nodal irradiation and total nodal irradiation with six courses of chemotherapy. Adjuvant chemotherapy significantly improved disease-free survival for patients classed as IA and IIA, IIIA, and IIIB but did not increase freedom from progressive disease for those classed as IB and IIB. Effects on survival are more difficult to evaluate as there have been fewer deaths, and many of the results of statistical tests do not reach significance. With the Gehan test significance is achieved only by the symptom-free group of patients, though the more sensitive Cox test shows significance for all patients together. These borderline survival advantages in symptom-free patients have taken 10 years to appear and are the result of a prolonged and difficult treatment regimen. In addition to the immediate toxicity the treatment has produced sterility in men¹⁷ and is associated with secondary malignancies.^{18 19}

As extensive radiotherapy may not be required in combination with chemotherapy these studies were discontinued in 1974 and new studies were started in which radiotherapy of the affected areas and chemotherapy were compared with subtotal lymphoid irradiation. A preliminary paper²⁰ at five years reported excellent survival and freedom from relapse in both groups in this study, but longer observation is required.

Since the introduction of adjuvant chemotherapy for stages I-III some have suggested that such patients might be treated with chemotherapy alone. A preliminary report²¹ of a study comparing chemotherapy and radiotherapy with chemotherapy alone was made last year. Of 13 patients who received chemotherapy alone three were reported to have relapsed (confirmed by personal communication), although when the abstract was prepared only one had. The British National Lymphoma

Group²² have compared chemotherapy with total lymphoid irradiation in stage IIIA patients. Although the initial complete remission rate and disease-free survival was inferior in the chemotherapy group, there was no difference in overall survival and longer follow-up is necessary. Chemotherapy alone for early-stage disease remains experimental, and such results should discourage its use until it has been thoroughly evaluated in controlled studies.

Problem of secondary malignancies

Recent studies have highlighted the problem of secondary malignancies in patients treated for Hodgkin's disease. In the Stanford series¹⁸ the actuarial estimate of the incidence of acute non-lymphoblastic leukaemia at seven years for patients receiving irradiation and chemotherapy was 3.9%. The high incidence of leukaemias in patients receiving both chemotherapy and irradiation is seen in other large studies^{23, 24} and strongly suggests that leukaemias are induced by the treatment and are not a part of the natural history of Hodgkin's disease. Most recently, non-Hodgkin's lymphomas have been reported in patients treated for Hodgkin's disease.¹⁹ Nitrogen mustard and procarbazine are the most likely leukaemogenic drugs in the MOPP chemotherapy regimen, and Valagussa *et al*²⁵ have reported 'that the ABVD regimen (adriamycin, bleomycin, vinblastine, and dacarbazine) does not induce leukaemias even when combined with irradiation.

Attempts to reduce the acute toxicity of the MOPP regimen has been made. The nausea and vomiting caused by nitrogen mustard remains a problem, and Kaye *et al*²⁶ have reduced this by substituting chlorambucil for nitrogen mustard, with results that are comparable to MOPP. No randomised comparison, however, has been undertaken, and follow-up is too short for survival to be adequately assessed. ABVD, as initial treatment, causes somewhat less nausea and vomiting than MOPP, but there is the added certainty of total alopecia and the longer-term risks of adriamycin cardiomyopathy and bleomycin pneumonitis.

The past decade has seen consolidation of the advances in treating Hodgkin's disease made in the 1960s. Although combined-modality treatment and selection of new subgroups within the Ann Arbor classification, together with new and less toxic chemotherapy, are likely to improve the results of treatment, the changes in management that are needed cannot yet be identified with certainty. Because of the improved results in Hodgkin's disease, survival is the only basis for judging new treatments, and we must wait 10 or more years before the results of studies are available.

Hodgkin's disease, has become a complicated problem of management that is best treated in specialist centres possessing experience in the many branches of medicine needed for optimal care. Despite advances, new clinical trials are still needed to refine treatment further. The main challenges are to define subgroups of patients who will benefit from combined-modality treatment, to reduce the acute toxicity of chemotherapy, to reduce the long-term effects of chemotherapy (especially second malignancies and sterility), and to design more effective chemotherapy regimens for patients who fail to respond to standard treatment. Answers to the questions can be obtained only from controlled studies testing the initial management, the effectiveness of salvage after relapse, and assessing the long-term toxicities of new treatments.²⁷

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The green parts of potatoes contain solanine, which is poisonous. Do the similar green parts found in exposed carrots also contain solanine with similar poisoning properties?

The carrot belongs to the umbell family of plants (which includes parsnip, celery, and chervil) and is phylogenetically distinct from the solanum family (potatoes and tomatoes). No toxic alkaloids have been isolated from carrots, and the green coloration found in exposed parts of the root is due to production of chlorophyll, which is non-toxic.