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Controversies in the Management of Hodgkin's Disease

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INTRODUCTION

ALTHOUGH THE treatment of Hodgkin's disease (HD) over the past decades has been a success when viewed from other areas of oncology and haematology, 20–40% of the patients still die from the disease. Considerable controversy exists in the treatment strategy and further progress is needed in the understanding of the aetiology and biology of the disease, in the methods of treatment and — of particular importance — in the definition of risk groups that need a tailored treatment.

AETIOLOGY AND BIOLOGY

The aetiology of HD is still obscure and the cellular origin of the clonal Reed–Sternberg cells is unknown. A number of candidate cells has been proposed over the years — and discarded again: T- or B-lymphocyte, macrophage, dendritic cell, interdigitating cell, myelomonocytic cell and others [1]. A major problem has been that the involved lymph nodes only contain a low tumour cell number (1–2%) on a background of various normal, reactive cells. The methodology has been too crude to analyse the few Reed–Sternberg cells *in situ* and methods for isolation in large quantities have not been available. With development of more refined and sensitive methods in immunology and molecular biology, this situation is changing. Thus Stein *et al.* [2] using antibodies against the β-chain of the T-cell receptor and B cell antigens demonstrated lymphocyte predominant HD to represent a B cell neoplasm, while the other types were either of B or T lymphoid origins (Table 1). Furthermore it was shown, that among 198 cases of HD 57% contained Epstein–Barr virus (EBV) genome as detected with the sensitive polymerase chain reaction. In other studies it had been shown by *in situ* hybridisation that the EBV genome was present in the tumour cells, but not in the surrounding reactive cells and that it was monoclonal, thus having entered the tumour cells prior to clonal expansion. In model experiments EBV infection of progenitor B cells and pre B cells led to a combination of genotypically early and phenotypically late (expression of activation markers) B cells, the pattern characteristic for Hodgkin's cells.

These findings indicate a role for a viral infection early in the process of malignant transformation, but whether EBV is the aetiologic agent or is superimposed on other aetiological agents is not clear. Probably several closely related aetiological patterns exist, resulting in the well described clinical spectrum of the disease.

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STAGE I-II

Treatment

In early stage HD the empirically developed methods of treatment are megavoltage large-field radiotherapy or combination chemotherapy or both. The optimal choice is still under debate.

In a recent international workshop on the treatment strategy in Hodgkin's disease the organising committee had collected data from 20 clinical centres in Europe and USA, a total of 14 000 patients with Hodgkin's disease [3].

The overall survival of 9090 clinical stage I-II patients was 60–71% at 15 years, thus leaving ample room for improvement. 50–60% had been treated with radiotherapy alone and 30–40% with radiotherapy plus combination chemotherapy. Both strategies led to a high response rate, 94–98%, but the relapse rate differed markedly with treatment: 30–50% after radiotherapy with or without low grade chemotherapy and 10–15% after radiotherapy plus combination chemotherapy.

The workshop had included both randomised and non-randomised trials, and the selection criteria for the treatment programs were not available. It is therefore necessary to validate the data also by looking at examples of the prospective trials included in the workshop, such as our National Danish Hodgkin Trial [4].

From 1972 to 1983 all previously untreated patients in Denmark with supradiaphragmatic Hodgkin's disease stage I and II as confirmed by laparotomy were entered into the trial. A total of 317 patients were randomised to receive either radiotherapy alone (mantle plus inverted Y field) or radiotherapy plus chemotherapy (mantle followed by 6 cycles of mechloroethamine/vincristine/procarbazine/prednisone (MOPP) chemotherapy). At a recent analysis 34% of the patients in the radiotherapy group and only 7% in the radiotherapy plus chemotherapy group had relapsed. This compares well with the above mentioned total result from the workshop where the inclusion also of non-laparotomised patients increased the relapse rates. The question then is: does the higher relapse rate

Table 1. Proposed cell of origin in Hodgkin's disease

Prior to 1987	1987–1990
Lymphoid cell	
Macrophage/histiocyte	LP: B cells
Myelomonocytic cell	
Dendritic cell	MC: B or T cells
Interdigitating cell	NS:
Sinus endothelial cell	
Megakaryocyte	

LP = lymphocyte predominantly, MC = mixed cellularity, NS = nodular sclerosis.

Table 2. Treatment of early stage Hodgkin's disease

Response		Relapse	Survival
RT	NS	High (30–50%)	NS? or RT + CT > RT
RT + CT		Low (5–15%)	

RT = radiotherapy, CT = chemotherapy, NS = not significant.

Table 3. Prognostic factors of early stage Hodgkin's disease

History	Multivariate analysis [5]
Age	
Stage	
B symptoms	Tumour burden
No. regions	Treatment
Bulky mass	
Tumour burden	
Sex	
Histology	
SR	
Treatment	

following radiotherapy alone lead to decreased survival and should all stage I-II patients therefore receive radiotherapy plus chemotherapy?

It turned out — as in other similar series — that most of the patients relapsing after radiotherapy could be induced into a new complete response with chemotherapy and their survival correspondingly improved.

In the Danish trial the overall survival now shows a trend in favour of radiotherapy plus chemotherapy, but there is no significant difference between the two groups. In the workshop results a similar trend was found towards better survival with the combined treatment, but only significantly different for the stage I-II patients. (15 yr survival for 630 radiotherapy patients 57%, for 926 radiotherapy plus chemotherapy patients 68%.)

An attempt to give a final answer to the question of a possible survival benefit from combined therapy is now being made in an international meta analysis of all randomised trials (organised by L. Specht and R. Peto).

Prognostic factors

Other types of analyses attempt to define subgroups of patients characterised by factors associated with poor prognosis (giving indication for more intensive therapy). In stage I-II disease in particular, bulky intrathoracic disease, number of involved regions, stage, B-symptoms, sex, histological subtype and erythrocyte sedimentation rate have been identified and it is obvious that many of these are interrelated.

Table 4. Treatment failures, stage III-IV

Type	Treatment
Dominant, resistant tumour line	Early shift to non-cross resistant combination
Non-dominant resistant tumour line	Alternating cycles different combination chemotherapy
Sensitive tumour line, inadequate therapy	Increase dose-intensity

Table 5. GM-CSF in Hodgkin's disease

WBC ≤ 2.0 × 10⁹/l		Neutrophils ≤ 1.0 × 10⁹/l	
With GM-CSF	Without GM-CSF	With GM-CSF	Without GM-CSF
0.8 days	6.3 days	1.0 days	5.4 days

Mean of 3 cycles.
WBC = white blood cells.

In the Paris workshop in 1989 very large patient numbers were available for analysis, but problems included that prognostic factors in many studies had been part of the selection process for the trial, and that important information, e.g. on measurements of tumour burden, had not been collected.

In the Danish National Hodgkin Study a careful assessment of size and localisation of all nodes was done and it was possible to enter these tumour sizes into an added total tumour burden of each patient. The patients were in the final analysis divided into 4 groups of equal size based on tumour burden, and these four values went into the multivariate analysis together with all the above mentioned biological factors. The result showed that with respect to disease-free survival, tumour burden and treatment were by far the most important prognostic factors and with respect to survival from Hodgkin's disease only age and tumour burden were independently significant [5].

Since tumour burden is easy to measure it could well be the single factor determining our treatment choice rather than, for example, Ann Arbor stage.

STAGE III-IV HODGKIN'S DISEASE

Treatment

It is generally accepted that combination chemotherapy is the treatment of choice in stage III B and IV disease and even in stage III A. Several series have failed to show a role for radiotherapy except for bulky disease, e.g. in mediastinum.

Combination chemotherapy has since 1970 been based on the MOPP program and in recent years on some alternatives, mainly doxorubicin/bleomycin/vinblastine/dacarbazine (ABVD). The Paris workshop had collected 872 patients. In stage III B and 1294 in stage IV who were treated with combination chemotherapy without radiotherapy. The CR frequency was 67% and 59%, respectively, with a 10 year relapse-free survival for CR patients of around 56%.

How can these far from impressive results be improved? There are two explanations for the failures: resistant tumour cell lines present at the onset of therapy and primary sensitivity but inadequate doses and rate of delivery of chemotherapy.

Resistant tumour cell lines can in a biologically "old" tumour have overgrown the sensitive clone, and in that case the patient does not respond to initial chemotherapy. In other patients the resistant clone is a minor fraction, but its constant growth despite treatment determines the timepoint for relapse. According to this Goldie–Coldman model an effective treatment in the first case would be a rapid shift to non-cross resistant drugs and in the latter case to use the primary combination regimen together with a combination of non-cross reactive drugs, preferably

simultaneously or — since this is not possible due to the side-effects of the presently known cytostatic agents — in alternating cycles.

The clinical studies that come closest to testing this hypothesis are those comparing MOPP to ABVD to MOPP alternating with ABVD. While the results from the Milan trial of MOPP vs. MOPP/ABVD [6] reported significant improvement with the alternating regimen, a recent prospective CALGB trial in which we have participated demonstrated that both ABVD alone and MOPP/ABVD compared to MOPP led to significantly better CR rates and failure-free survival at 3 years (ref. 7, updated by J.R. Andersen at the Paris workshop 1990 [3]). The improvement therefore seems to be the ABVD regimen rather than the principle of alternating cycles. The next questions then are whether each of the ABVD drugs is more effective than each of the MOPP drugs,if there is an unknown synergy in the combination or if it is a question of dose. A ranking of the single drugs with respect to activity against HD would require single agent prospective comparative trials in previously untreated patients, and this is not possible. The limited information we have would not favour either of the two combinations and a difference in synergistic effect of the drug combinations has not been documented. A reasonable explanation may therefore be a better tolerance of the ABVD regimen, and therefore a higher dose intensity (actual dose/time unit). This was in fact seen in the above described CALGB trial, where the dose reduction through the study was significantly larger with MOPP than with the two other regimens.

In an earlier CALGB trial of MOPP vs. BOPP (B = BCNU) we noted a constant decrease in tolerated doses throughout the 6 cycles and by cycle 6 the doses were down to nitrogen mustard 60%, vincristine 65%, procarbazine 55% of the prescribed dose in the standard MOPP programme [8].

With knowledge of the steep dose response curves of most cytostatic agents *in vitro* and in animal experiments and the clinical experience of decreasing drug tolerance throughout the chemotherapy cycles, it seems that we have a reasonable explanation for a large fraction of the failures, and methods for improving clinical drug tolerance and drug delivery schedules should have high priority.

Colony-stimulating factors

How can we increase dose intensity without increasing the host toxicity? For drugs such as vincristine, where the main side-effect is neurotoxicity, we have at present no prophylactic means. An increase in delivered dose can only be accomplished by accepting a higher degree of neurotoxicity. For the myelotoxic drugs, neutropenia (and accompanying infection) and thrombocytopenia (and accompanying bleeding) are the main dose-limiting side effects, and antibiotics and platelet transfusions have so far been the only therapeutic interventions. With the introduction of the haemopoietic growth factors (colony stimulating factors) into clinical trials, this situation seems to change.

Colony-stimulating factors (CSFs) are a group of physiologically occurring glycoproteins that are necessary for the survival, proliferation and differentiation of haemopoietic progenitor cells [9]. The genes for most of the factors have been cloned and by recombinant techniques sufficient quantities can now be made for clinical purpose. Erythropoietin has already an established role in nephrogenic anaemia and the two myeloid growth factors G-CSF (G = granulocyte) and GM-CSF (GM = granylocyte-macrophage) are now in clinical trials. The next factors for clinical use, M-CSF, interleukin-3 and interleukin-6 are in the preclinical phase.

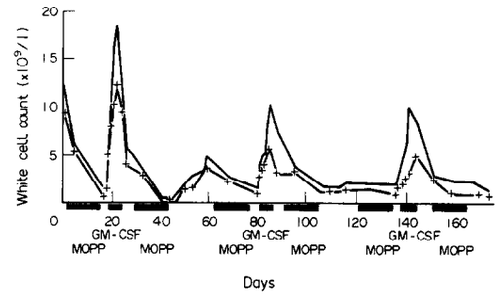

Fig. 1. Effect of GM-CSF, 8 μg/kg subcutaneously, on white cell count in Hodgkin's disease patient treated wth MOPP. —— = white cell count and +—+ = neutrophil count.

Following the reports of initial clinical experience, demonstrating high tolerability and effective bone marrow stimulation [10, 11], we initiated a study of GM-CSF in previously untreated patients with Hodgkin's disease, who were planned for standard MOPP chemotherapy. The purpose of the study was to examine the optimal dose level and method of administration of GM-CSF and to examine effect on HD and on chemotherapy toxicity and delivery.

GM-CSF (glycosylated CHO material, Schering Plough/Sandoz) was given daily for 5 days on days 17–22 in MOPP cycle 1, 3 and 5, the patient thus being his own control in the other series. 6 patients were treated at each of the dose levels 2, 4, 8 and 16 μg/kg and were randomised to receive the drug either subcutaneously twice daily or continuously intravenously. The results proved GM-CSF to be highly effective with significantly higher leucocyte and neutrophil counts (and area under the curve) in the GM-CSF cycles than in the control cycles [12] (Fig. 1).

Thus also fewer days of neutropenia were seen (Table 5), and the recovery of WBC/neutrophil count after chemotherapy was faster. Of especial importance were the day 29 counts, which in the 8 and 16 μg/kg groups allowed the subsequent MOPP cycle to be given on time and in full dose, while significant dose reductions and delays were noted in the control cycles and in historical controls.

The study of dose levels proved the 2 μg/kg dose to be inferior to 4, 8 and 16 μg/kg, but since adherence to the chemotherapy schedule was best after 8 and 16 μg/kg and since 16 μg/kg led to significantly more toxicity, we recommend 8 μg/kg as the optimal dose. Subcutaneous administration was preferable to continuous intravenous infusion due to improved results and convenience.

Since this study was a dose finding study where not all doses proved to be optimal and since GM-CSF was only given at every other cycle, the full effect with respect to increase in dose intensity can be stipulated to be significantly larger, than seen in our study. Prospective trials will have to be done to demonstrate whether the final goal, improvement in outcome for the patient, can be achieved by this therapy. In the near future similar trials with G-CSF, IL-3 and IL-6 and combinations of growth factors may give us new leads in the management of Hodgkin's disease.

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Controversies in the Management of Non-Hodgkin Lymphoma

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INTRODUCTION

NON-HODGKIN lymphomas (NHL) represent a disseminated group of malignancies with heterogenous morphological, immunological and clinical characteristics. The rapidly increasing knowledge of the pathophysiology and histology of the immune response and the understanding of lymphocyte differentiation has led to the concept that NHL represent neoplastic counterparts of reactions which usually take place after antigenic stimulation. The course of NHL ranges from well tolerated, indolent malignancies to quickly proliferating, rapidly fatal tumours. Although much has been achieved, especially in the treatment of high-grade lymphoma, NHL are among the most challenging malignancies today. This paper intents to summarise some of the important issues and controversies in the management of NHL.

CLASSIFICATION

The classification of neoplastic lymphoid disorders has undergone substantial changes over the last decades. Since its introduction in 1956, the Rappaport classification [1] had been widely accepted as an easy reproducible and clinically relevant system. However, the validity of this classification became questionable when the functional and ontogenetic heterogeneity of the normal immune system was discovered. Consequently other classifications have been proposed, including those by Dorfmann [2], Bennet [3], Lukes and Collins [4], Lennert [5], and the WHO [6], but none have become widely accepted. The use of six different classifications for NHL throughout the world obviously made international analysis and comparison of clinical trials extremely difficult.

In an attempt to find a terminological compromise for the definition of entities that differed considerably regarding clinical course, prognosis and therapeutical implications, the so-called "working formulation" was introduced in 1982 [7]. The working formulation (Table 1) was not created as a new classification but as a means of translating one classification into another. It was based on the clinical follow-up information of 1175 previously untreated cases by pathologists representing the six different major classification systems. Utilising morphological and clinical criteria, 10 subtypes of NHL were subdivided into three prognostic groups: low-grade (median survival of 7 years), intermediate-grade (median survival: 3 years), and high-grade (median survival: 1 year). Being a simple, practical translation formula for interinstitutional and international comparisons, the working formulation does not employ immunologic methods in the study design.

A European rival, the Kiel classification [8], is based on morphological criteria and incorporates information derived from immunological and molecular biological techniques. The Kiel classification (Table 2) in its recently updated form [9] separates the NHL according to the B- and T-cell origin. Its discrimination between only two major groupings according to clinical behaviour (low-grade and high-grade) has proved relevant in determining treatment [10] although the identifi-

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