Outcome in Hodgkin’s disease: A 20-year cohort of patients

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SUMMARY
We reviewed the long-term survival, treatment-related mortality and morbidity of a continuous cohort of patients with Hodgkin’s disease diagnosed and staged at the Haematology unit of the Belfast City Hospital between January 1973 and October 1992. The analysis included a comparison of the survival of those patients who were entered into BNLI (British National Lymphoma Investigation) trials compared to those not entered during this 20 year period. In addition univariate and multivariate analysis of prognostic factors was performed.

The complete remission rate (CR) was 79.6% with a 15 year survival of 55.3%. On multivariate analysis in which deaths due to active Hodgkin’s disease only were considered age >50 emerged as the most significant prognostic factor (P<0.0007), the presence of B symptoms also having independent significance (P=0.008). Trial status did not have any independent prognostic significance. Eighty one deaths occurred: active Hodgkin’s disease (50), second malignancy (9), treatment-related (10), unrelated (9), unknown (3).

This long-term follow up study provides useful information additional to the data produced by clinical trials which are biased by selection criteria. The occurrence of Haemophilus Influenzae meningitis in a patient 17 years following splenectomy highlights the need for appropriate vaccination of patients splenectomised for Hodgkin’s disease.

INTRODUCTION
It is now 166 years since Thomas Hodgkin published his original article “On some morbid appearances of the absorbent glands and spleen”, in which he described six cases of a condition which he believed to be a specific disease entity. Within the last century Hodgkin’s disease has emerged as a curable malignancy due to the efficacy of megavoltage radiotherapy, combination chemotherapy, and more recently marrow ablative chemotherapy followed by stem cell grafting. The survival of patients today has dramatically improved when compared with that of untreated patients, whose five-year survival was reported to be 5.6%. With the advent of kilovoltage radiotherapy in the 1920’s this figure rose to 51%, and a further significant survival increment (73.3% at 5 yrs) resulted from the use of megavoltage radiotherapy in the 1950’s. Within the last 3 decades the use of combination chemotherapy and combined modality therapy has improved survival with approximately 85% of patients alive at five years.

Such survival data is mainly obtained from the results of clinical trials, which are designed to evaluate different therapeutic regimens in strictly equal patient cohorts, a process which necessitates the use of inclusion/exclusion criteria. This inherent selection process means that clinical trials cannot assess the real survival probability of all patients with a specific disease. For this reason single centre outcome studies are an important means of determining survival outcomes in unselected cohorts of patients. This study was undertaken primarily to ascertain the long-term survival of all patients suffering from
Hodgkin’s disease who were diagnosed and staged at the Belfast City Hospital over a twenty year period. Secondary objectives were to compare the survival of those patients entered into BNLI trials with those patients who for various reasons were not, to assess the delayed effects of treatment to identify the various causes of death and to investigate those factors which adversely affected survival in this continuous cohort of unselected patients.

METHODS

We reviewed the case notes of 209 consecutive patients with previously untreated Hodgkin’s disease who were diagnosed/staged in the Haematology unit of the Belfast City Hospital from January 1973 to October 1992. One hundred and twelve of these patients had been entered into various BNLI trials, following acceptance of the histological diagnosis by the BNLI panel.

Pathology review

Limited resources prohibited histological review of all the 89 non-trial patient’s diagnostic biopsies, but a local panel of pathologists was formed to review the original histology of any of the non-trial patients in situations known to be associated with diagnostic difficulty (i.e. original diagnosis had been made on extranodal tissue, original histology had not been classified using the Rye classification, a second biopsy had questioned the original diagnosis, a second malignancy had been diagnosed simultaneously (within 6 months).) These criteria identified 18 cases for review and with the additional aid of immunocytochemistry a diagnosis of non Hodgkin’s lymphoma was favoured in four cases, myeloproliferative disorder in two, and non-diagnostic in two, leaving a total of 201 cases for analysis.

Patients

The characteristics of the patient population (N=201) which includes two sets of siblings are shown in Table I. The median age was 32 (range 9 to 81), with the usual male preponderance being noted.

Staging method

Patients had been staged in accordance with BNLI protocols. Routine staging investigations included: FBC with DWCC, baseline ESR, serum copper, lactate dehydrogenase, liver function tests, bone marrow examination and chest xray with or without tomography. Prior to 1981 lymphangio-

| Variable | Category | number | %  |
|----------|----------|--------|----|
| Sex      | male     | 125    | 62 |
|          | female   | 76     | 38 |
| Age      | <50      | 152    | 75.6 |
|          | >50      | 49     | 24.4 |
| Trial status | yes | 112 | 55.7 |
|          | no       | 89     | 44.3 |
| B symptoms | yes | 119    | 59.2 |
|          | no       | 82     | 40.8 |
| Stage    | I        | 38     | 19 |
|          | II       | 69     | 34 |
|          | III      | 58     | 29 |
|          | IV       | 36     | 18 |
| Histology| LP       | 15     | 7  |
|          | NS       | 130    | 65 |
|          | MC       | 40     | 20 |
|          | LD       | 12     | 6  |
|          | U        | 4      | 2  |
| Laparotomy status | yes | 75    | 37 |
|          | no       | 126    | 63 |
| Lymphangiography | yes | 61    | 30.3 |
|          | no       | 140    | 69.7 |

LP=Lymphocyte predominant  
NS=Nodular sclerosis  
MC=Mixed cellularity  
LD=Lymphocyte depleted  
U=Unclassified

graphy with or without abdominal ultrasound was used to detect infradiaphragmatic disease, and following these investigations patients with apparently localized disease and absence of B symptoms (fever, night sweats and/or unexplained loss of 10% of body weight) who would have been suitable candidates for local radiotherapy routinely underwent staging laparotomy with splenectomy, wedge liver biopsy, and biopsy of suspect abdominal glands. Since then the increasing use of CT scanning of the thorax, abdomen and pelvis effectively made lymphangiography and laparotomy redundant as it became clear that staging laparotomy had no impact on survival owing to the effectiveness of salvage chemotherapy for patients relapsing after initial radiotherapy.

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Patient treatment

The patients entered into the BNLI trials were treated according to trial protocols. Localized disease was treated with either local or regional radiotherapy of the mantle (MR) or inverted Y type, and some patients with stage III disease received total nodal irradiation (TNI). More advanced stage disease was treated with combination chemotherapy regimens: mustine, vincristine, procarbazine and prednisone (MOPP); chlorambucil, vincristine, procarbazine and prednisone (LOPP); or doxorubicin, vinblastine, etoposide and prednisone (EVAP). In more recent years the intensive regimen consisting of carmustine, etoposide, cytarabine and melphalan (BEAM) followed by autologous stem cell transplantation has been used. Eleven patients in this cohort have undergone autologous transplantation using bone marrow or peripheral blood stem cells.

The remaining patients who were not entered into BNLI trials were treated in a similar fashion - radiotherapy for localized disease without B symptoms, and combination chemotherapy regimens similar to the above.

Twenty four patients following initial staging were treated and followed up at two other centres: The Northern Ireland Centre for Clinical Oncology and Radiotherapy (22 patients), and Craigavon Area Hospital (two patients).

Response to treatment and patient follow-up

The clinical notes were studied to reassess the response to treatment at the completion of therapy. Criteria for complete remission (CR) were disappearance of all clinical, biochemical and radiological evidence of disease, and if CR occurred it was dated from the completion of therapy. Rates of relapse and subsequent attainment of second, third, and fourth remissions were recorded. Complications of the disease or its treatment such as sepsis, infertility, second malignancy, herpes zoster, cardiac and respiratory sequelae were documented.

Follow-up information on all patients was obtained by telephoning the general practitioner, or by means of a written questionnaire. Information on patients no longer living in Northern Ireland was sought from the haematology-oncology centre responsible for patient care. Death certificates and post-mortem reports were studied, and causes of death were categorized as Hodgkin's disease-related, treatment-related, second malignancy, other causes, or unknown. In 200/201 cases overall survival was measured from the date of histological diagnosis to the date of death or to September 1st, 1993 (date of study commencement), with one patient being lost to follow-up after 6 years of observation.

Statistical Analysis

Statistical analysis was carried out using SPSS software. Survival was calculated using the life table method of Kaplan and Meier. In the analysis of prognostic factors deaths due to active Hodgkin's disease only were included. Unrelated and second malignancy deaths were disregarded as were early deaths during induction chemotherapy, most of which were due to chemotherapy-induced sepsis. Comparisons in univariate analysis were performed using the log rank test. Factors which reached significance on univariate analysis were analysed using a stepwise Cox proportional hazards regression. A final model was obtained containing only those factors which maintained independent prognostic significance.

RESULTS

Response to treatment

The CR rate was 79.6% (160/201) and the majority of these patients (111) did not relapse. Of the 49 patients (31%) who relapsed approximately half went on to achieve second CR (25/49). Second relapse occurred in nine of these 25 patients (36%), five of whom successfully achieved third CR, and one patient achieved fourth CR. Patients who achieved CR were significantly younger than non-remitters (P<0.001).

The majority of first relapses (45/49) occurred within five years of the completion of therapy, with only one relapse beyond 10 years and remainder between 5-10 years.

Survival

The overall survival for the 201 patients is shown (Fig. 1) which includes deaths from all causes. The 10 and 15 year survival rates were 61.3% (confidence interval 54 to 68.6) and 55.3% (confidence interval 47.2 to 63.4). The median period of follow-up was 7.4 years for all patients, and 11.6 years for those patients still alive. Survival for patients who achieved CR was significantly better than non remitters (P<0.0001).
Viral Infections

Herpes zoster infection occurred in 41 patients (21%) during the period of hospital follow-up, and three of these patients had disseminated zoster.

As previously mentioned a fatal case of herpes simplex encephalitis occurred.

Fertility Status

Infertility post chemotherapy/radiotherapy was only documented in eight patients, four male (3 of whom had received MOPP or LOPP, and one who had received TNI + LOPP), and four female (one having received LOPP and EVAP, one TNI, and the remaining 2 patients BEAM chemotherapy. In contrast 8 female patients who received combination chemotherapy have subsequently become pregnant.

Analysis of prognostic factors influencing survival

Univariate

The results of univariate analysis are shown in Table II. Age >50 (P<0.0001), elevation of the baseline ESR >50 mm/hr (P=0.0001), and elevation of the baseline serum copper (P=0.0009) emerged as the most significant factors influencing survival. There was a trend towards improved survival for patients entered into trials but this did not reach statistical significance (P=0.08). In this analysis the following factors were found not to be significant: sex, absolute lymphocyte count <1.5 x 10^9/L, elevation of the serum LDH, mediastinal involvement, histological subtype, and treatment period 1973-1981 vs 1982-1992.

Multivariate

Two factors alone age >50 and the presence of B symptoms maintained independent prognostic significance (Table II). Elevation of the baseline serum copper approached significance (P=0.056).

Figure 2 shows that the survival of trial patients from Belfast is very similar to that of trial patients from other UK centres (G Vaughan Hudson, personal communication).

Causes of death

Eighty one deaths occurred, the majority of which (n=50) were due to active Hodgkin’s disease. Ten deaths were treatment-related, including two splenectomy-related deaths: one early death due to subphrenic abscess and haemorrhage from multiple acute gastric ulcers; and one death due to Haemophilus influenzae meningitis occurring 17 years following splenectomy in a stage IA patient. Infection was a major contributing factor in the remaining treatment-related deaths with several deaths from gram-negative sepsis, and one death from herpes simplex encephalitis. Nine patients died from unrelated causes: trauma 3, myocardial infarction 3 (2 in CR, 1 prior to treatment), pulmonary embolism 1, stroke 1, bronchopneumonia in CR 1. In three cases the cause of death could not be accurately determined.

Second malignancy developing between 0.3-18 yrs (median 4 years) resulted in the death of nine patients (respiratory 4, gastro-intestinal 3, lymphoblastic lymphoma 1, undetermined 1).

Other complications of the disease or its treatment

Figure 2. Survival of Belfast trial patients compared to trial patients from other BNLI centres.

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### TABLE II

Analysis of prognostic factors influencing survival

| Factor          | category | numbers | Univariate | Multivariate |
|-----------------|----------|---------|------------|--------------|
|                 |          |         | Significance (P) | Significance (P) | relative risk | 95% CI    |
| Age             | <=50     | 152     | <0.0001    | 0.007        | 2.73         | (1.31-5.7) |
|                 | >50      | 49      |            |              |              |           |
| B symptoms      | no       | 82      | <0.0001    | 0.008        | 3.79         | (1.4-10.2) |
|                 | yes      | 119     |            |              |              |           |
| Copper          | <=26.7   | 71      | 0.0009     | 0.056        | 2.33         | (0.97-5.58) |
|                 | >26.7    | 81      |            |              |              |           |
| ESR             | <=50     | 102     |            |              |              |           |
|                 | >50      | 74      | 0.0001     |              |              |           |
| Trial status    | yes      | 112     |            |              |              |           |
|                 | no       | 89      | 0.08       |              |              |           |
| Albumin         | >=35     | 98      |            |              |              |           |
|                 | <35      | 47      | 0.0147     |              |              |           |
| Alkaline phosphatase | <=280  | 74      |            |              |              |           |
|                 | >280     | 71      | 0.02       |              |              |           |
| Bone marrow involvement | no | 163     |            |              |              |           |
|                 | yes      | 19      | 0.003      |              |              |           |
| Stage 4         | no       | 165     |            |              |              |           |
|                 | yes      | 36      | 0.0007     |              |              |           |
| Hb<10           | no       | 165     |            |              |              |           |
|                 | yes      | 23      | 0.0042     |              |              |           |
| Platelets       | 150-400  | 118     |            |              | 0.096        |           |
|                 | >400     | 59      |            |              |              |           |

Analysis includes only deaths due to active Hodgkin's disease (N=50)

Comparison of the trial patients with the non-trial patients

Trial patients were a significantly younger cohort (P=0.028). Univariate analysis showed a trend towards longer survival in the trial patients but this did not reach statistical significance.

**DISCUSSION**

Long term follow-up studies in curable malignancies are essential to enable clinicians to assess treatment-related morbidity and mortality and subsequently modify treatment protocols in order to minimize unwanted sequelae, without jeopardizing the prospect of cure. The survival data from studies such as this provide a full assessment of the efficacy of treatment and the morbid consequences of it, and are a source of valuable information which can be subjected to meta-analysis. Our survival rates are very similar to the results of the relatively few centres that have investigated long term survival in a consecutive group of patients, to the figures produced by the international data base on Hodgkin's disease and to the BNLI data for other trial centres (Vaughan Hudson G, personal communication). An improved outcome for patients managed in comprehensive cancer centres rather than in general hospitals has been recorded. Our data suggests that the benefit of trial participation is not restricted to those patients...
randomized into clinical trials but that it reaches the nontrial cohort in the participating centre, a finding noted in the management of patients with myeloma in Finland.13

The knowledge of important prognostic factors has significantly modified the staging and treatment of Hodgkin's disease in the past two decades. Advanced age is commonly found to be a highly significant adverse factor on multivariate analysis,5, 6, 8-11 as is the occurrence of B symptoms.5, 14 In our method of analysis of prognostic factors we have disregarded not only unrelated and second malignancy deaths but also early induction deaths, the majority of which were due to chemotherapy-induced sepsis, believing such deaths to relate to random unpredictable events possibly related to variability of marrow depression secondary to chemotherapy and/or variability in depression of cellular immunity. When this method of analysis is applied, only the factors of advanced age and the presence of B symptoms maintain independent significance, with elevation of the serum copper approaching significance.

Elevation of the serum copper in Hodgkin's disease was first described in 1957,15 and since then it has been infrequently mentioned in the literature.16-20 In this study elevation of the serum copper approached significance on multivariate analysis. We feel that further evaluation of the prognostic significance of this variable in a larger number of patients would be interesting in order to clarify its status as an independent prognostic factor.

Active Hodgkin's disease caused the majority of deaths 50/81 (64%) in this series, and this correlates closely with data from previously published series,4 and with data produced from the international data base on Hodgkin's disease11 in which 14,225 patients were registered. Nine of our patients developed second malignancy (4.5%) which is similar to the findings of other authors.8, 21-23 and the latter three authors have calculated that up to a 6 fold excess risk of all second cancers exists in patients treated for Hodgkin's disease when compared to general population incidence data. Advanced age at the time of diagnosis has been associated with an increased incidence of second malignancy,11, 22, 23 and combined modality therapy has also been implicated.22, 24 The occurrence of acute myeloid leukaemia has been reported between 0.4%-10 % of patients,8, 24 yet no cases have been seen in this series to date. This may be due to the low use of MOPP therapy in this cohort, as MOPP therapy alone or in combination with radiotherapy has been shown to be a significant predisposing factor.

Two laparotomy-related deaths occurred in this series, one of which was due to Haemophilus influenzae meningitis occurring 17 years following splenectomy in a patient in continuing first remission, and this 1.3% incidence of fatal sepsis post splenectomy is similar to that reported by Mazza et al in his series of 570 patients.9 During the course of this study we were able to identify 47 living asplenic patients whose vaccination status was unknown, we subsequently contacted their general practitioners with a view to having them appropriately vaccinated against Pneumococcus and Haemophilus influenzae type B in accordance with recently published guidelines.25

Infertility was documented in eight patients during the period of hospital follow-up, five of whom had received MOPP, which has been implicated as a major cause of gonadal dysfunction;26 in contrast live births occurred in eight patients following treatment with combination chemotherapy (MOPP or LOPP). Fertility status proved very difficult to assess accurately as although data on female patients is relatively easily obtained from the hospital or primary care notes, fertility status on male patients is difficult to determine unless semen analysis following therapy has been performed. In addition, pregnancies in the partners of male patients are not usually recorded in the patients' notes, and without DNA testing paternity cannot be confirmed.

In this study we did not demonstrate a significant improvement in survival in patients treated from 1982-1992, compared to patients treated in the earlier period prior to 1982, and this has also been the finding of the international data base on Hodgkin's disease,11 so there is still room for considerable improvement in long-term survival, but how will this be achieved? The major factors identified as contributing to mortality were sepsis, second malignancy, unresponsive disease, and disease relapse. The marked reduction in the use of staging laparotomy should reduce the risk of death in complete remission by lowering the incidence of post-splenectomy sepsis. The use of recombinant human granulocyte-colony

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stimulating factor (G-CSF) in selected patients should reduce the risk of sepsis during the neutropenic phase following chemotherapy. Deaths from second malignancies should also decline with the decreasing use of MOPP type chemotherapy. Patients with unresponsive disease constitute around 10% in most series, and this figure must be reduced in order to improve survival. Most centres are currently using intensive regimens such as BEAM followed by autologous stem cell transplant for patients with refractory and relapsed Hodgkin’s disease. For patients with resistant relapse the results so far are disappointing, with progression free survival at five years of only 19.2% so perhaps new chemotherapeutic agents will be required to alter CR rates significantly. However a longer period of follow up is necessary to balance fully the benefits of intensification with the long term complications of such treatment.

Results from the IDHD have shown that patients cured from Hodgkin’s disease have a relative risk of dying multiplied by 2.09 compared with the general population, and this confirms the need for long term follow-up studies in order to accurately document causes of death and alter treatment protocols to reduce the excess risk of death in patients cured of their disease. This study also provides reliable survival data with follow up on 99.5% of the original cohort, which can be compared to the survival of the patients treated at this centre in the next century, in order to ascertain if apparent improvements in therapy translate into a durable survival advantage.

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