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Hodgkin's lymphoma in children aged 5 years or less – The United Kingdom experience

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ABSTRACT

Purpose: The aim of this study is to describe the natural history of Hodgkin's Lymphoma (HL) in a large unselected group of children aged 5 years or below at diagnosis, who were treated on a standard treatment programme in the United Kingdom between 1982 and 2000.
Methods: Eighty-one unselected children with HL aged 5 years or under at diagnosis, treated on the United Kingdom Children's Cancer Study Group (UKCCSG) Hodgkin's trials HD1 (1982–1992) and HD2 (1992–2000), were included in the study.
Results: Sixty-one patients (81%) presented with early stage disease ($n = 66$). Fifty-three patients (65%) received combination chemotherapy, 28 (34%) received involved field radiotherapy (IF-RT) and 4 patients were treated with combined modality therapy. Eighteen children relapsed after primary therapy.
Conclusions: Children treated with IF-RT had a higher rate of primary treatment failures as well as increased late treatment-related morbidity.

1. Introduction

The natural history of Hodgkin's lymphoma (HL) in the very young children (below the age of 6 years) remains largely unknown due to its rarity. Published studies of the disease in this age population are few and in all published series, reported patient numbers have been small.[1–3] In fact, in most publications of childhood HL, there is no separate analysis of treatment response or survival outcome for children in this age group. The aim of this study was to describe the natural history of HL in the very young and we report here the results of a large national group of unselected children aged 5 years or less who received a standard treatment programme between 1982 and 2000.

2. Patients and methods

2.1. Patients

All children with HL who were 5 years of age or under at the time of diagnosis and registered on the United Kingdom Children's Cancer Study Group (UKCCSG) HD1 and HD2

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trials were included in the study. The HD1 trial was conducted between 1982 and 1992 while HD2 ran from 1992 until 2000. Disease staging was according to the Ann Arbour system.[4] Staging procedures included clinical history, physical examination, chest X-ray, ultrasound of the abdomen and pelvis and computed tomography of chest and abdomen. Staging laparotomy was not performed routinely. Biopsy tissue morphology was classified as per the Rye criteria,[5] namely, lymphocyte predominant (LP), nodular sclerosing (NS), mixed cellularity (MC) and lymphocyte depleted (LD). There was no central review of radiology or staging. Histology was reviewed centrally in the HD1 trial and the concordance rate between the local pathology report and central review was >95%. However, there was no central review of pathology in the HD2 trial. Hence, institutional pathological reports and staging investigations were utilised. Relapse was documented where possible by biopsy if peripheral lymph nodes were involved; otherwise, unequivocal new radiological lesions were accepted as proof of relapse in the absence of another reasonable explanation.

Informed consent for treatment was obtained from the patients' parents or legal guardians in accordance with the local institutional and ethical committee guidelines. Followup information is available for all patients. The median followup duration for surviving patients is 8 years and 6 months (range 18 months–20 years).

2.2. Treatment strategy

In both trials, only patients with stage IA disease irrespective of the histological subtype had the option of being treated with either involved field radiation alone (IF-RT) or combination chemotherapy. The total radiation dose was 35 Gy delivered in 20 fractions (1.75 Gy/fraction; five times per week). All but two patients were treated with combination chemotherapy (CT) that consisted of chlorambucil 6 mg/m^2 orally on days 1–14, vinblastine 6 mg/m^2 intravenously on days 1 and 8, procarbazine 100 mg/m^2 on days 1–14 and prednisolone 30 mg/m^2 orally on days 1–14 (ChlVPP) administered at 28 day intervals. The total number of courses administered ranged from 6 to 10 depending on the time to achieve complete remission (CR). The trial recommendation for both HD1 and HD2 was n plus 4 cycles of chemotherapy where n is the number of cycles of chemotherapy to achieve CR. In the earlier HD1 trial, children with bulky mediastinal disease that exceeded one-third of the maximum chest diameter on posterior anterior chest X-ray were given consolidation mediastinal radiotherapy (20–35 Gy) at 6 weeks after the last course of chemotherapy. One patient received the VEEP regimen (vincristine 1.5 mg/m^2 on days 1 and 8, epirubicin 50 mg/m^2 intravenously on day 1, etoposide 100 mg/m^2 as an intravenous infusion over 1 h on days 1–5 and Prednisolone 60 mg/m^2 orally on days 1–8) and 1 patient received an alternating hybrid chemotherapy regimen of ChlVPP and ABV (doxorubicin 25 mg/m^2 as an intravenous infusion over 6 h on days 1 and 15, bleomycin 10,000 iu/m^2 intravenously on days 1 and 15 and vincristine 1.5 mg/m^2 on days 1 and 15).

2.3. Definitions of response

Complete response (CR) was defined as disappearance of all detectable clinical and radiological evidence of disease and disappearance of all disease-related symptoms that were present at diagnosis.

Partial response (PR) was defined as greater than 50% reduction in tumour or nodal volume.

Progressive disease (PD) was defined as appearance of any new lesion during treatment or increase in the size of more than 25% of the previously documented tumour volume in any one involved region and or recurrence of disease symptoms which cannot be explained otherwise during treatment.

2.4. Statistics

Actuarial survival (OS) and disease free survival (DFS) were calculated by the life table method of Kaplan and Meier[6] and the differences between the groups were assessed by means of the log rank test. To determine the independent prognostic significance on pre treatment factors on OS and DFS, multivariate analysis was conducted using the Cox proportional hazard model.[7] A step-up method was used and variables entered at the 0.05 level of significance. All calculations were performed with SPSS version 14 statistical software.

3. Results

3.1. Patient characteristics

A total of 81 patients aged 5 years or less were enrolled in both of the UKCCSG HD1 and HD2 trials (11% of the total 712 patients recruited). The demographic and clinical characteristics including the treatment details are listed in Table 1. In this subgroup, 46 (57%) patients were treated according to the HD1 protocol and 35 (43%) in accordance with the HD2. protocol. There was a male predominance with 63 (78%) boys and 18 (22%) girls. The median age at diagnosis for both the studies was 4 years; the youngest patient was 7 months old at diagnosis. Sixty-six (81%) children presented with either stage I or stage II disease. Nodular sclerosis (NS) was the most common histological subtype (36 of 81 patients, 44%) followed by the mixed cellularity (MC) subtype (n = 29; 36%). Lymphocyte predominant (LP) subtype was seen in 16 patients (20%) and all but one of these patients had early stage disease (stage I–12; stage II–3). Eighteen children had mediastinal disease at diagnosis of whom, 4 had bulky disease. Fifty-three patients (65%) received combination chemotherapy alone as first line therapy. Of the remaining twenty eight patients, 24 (30%) received involved field radiotherapy (IF-RT) alone, for stage IA disease and 4 children (5%) received a combination of chemotherapy and radiotherapy. The latter 4 received ChlVPP chemotherapy prior to IF-RT treatment. Overall, 95% (n = 77) of the children achieved complete remission (CR) after primary therapy. One patient with stage IV B disease in the HD1 trial had a refractory disease on ChlVPP and died of progressive disease and one patient died during the first course of chemotherapy due to a suspected underlying immunodeficiency disorder. The remaining two patients had residual radiological abnormalities at the end of primary therapy and were be-

Table 1 – Patient characteristics

	HD-1		HD-2		All	
Patients	46		35		81	
Sex						
Male:female	37:9		26:9		63:18	
Age (years)						
Median	4		4			
Stage	A	B	A	B	A	B
I	17	1	14	2	31	3
II	14	5	13	0	27	5
III	4	3	3	2	7	5
IV	1	1	0	1	1	1
Histology						
LD	1		0		1	
LP	8		8		16	
MC	19		10		29	
NS	18		18		36	
UC	–		1		1	
Initial treatment						
RT	16		8		24	
CT	27		26		53	
CMT	3		1		4	
Initial chemo						
ChlVPP	29		26		55	
VEEP	1		0		1	
ChlVPP/ABV	0		1		1	
DXT dose						
20 Gy (CMT)	1		0		1	
30 Gy (CMT)	2		0		2	
34 Gy	0		1		1	
35 Gy	16		8		24	
Response						
CR	43		34		77	
PR[a]	1[a]		1[a]		2[a]	
PRD	1		0		1	
NA	1		0		1	
Relapse	14		4		18	
Deaths	6		0		6	
Median FU	10 years and 2 months		6 years and 7 months		8 years and 6 months	

LP, lymphocyte predominant; LD, lymphocyte depleted; MC, mixed cellularity; NS, nodular clerosing; UC, unclassified; RT, radiotherapy; CMT, combined modality therapy; FU, followup; NA, not assessable.
a Complete remission unconfirmed.

lieved to be in unconfirmed complete remission (Cru) rather than in PR.

3.2. *Relapses*

Eighteen (22%) children relapsed after primary therapy. Seven of the 14 patients who relapsed in the HD1 trial had received IF-RT alone for stage IA disease while the remaining 7 had all received CT (Table 2). Of the 4 patients who relapsed in the HD2 trial, two had received IF-RT for stage IA disease while the two remaining patients (stage I–1 and stage III–1) had received chemotherapy. Thus, 50% (9/18) of patients who received RT for stage IA disease relapsed. All of the nine relapses occurred outside the radiation field. Table 2 lists the relapses according to stage and treatment.

Table 2 – HL relapses according to stage and treatment

	Stage				Treatment	
	I	II	III	IV	CT	RT
HD1 Trial	7	5	1	1	7	7
HD2 Trial	3	0	1	0	2	2
Total (%)	12	6	2	1	50	50

3.3. *Salvage treatment*

Of the eighteen patients who relapsed, 14 (78%) achieved a second CR and 2 (11%) a partial remission (PR) with salvage CT. One patient had died of disease progression following relapse with no response to subsequent treatment and one patient died of an infection after relapse. Four patients underwent high dose therapy followed by autologous stem cell transplantation (ABMT) of whom 3 remain in CR. Salvage chemotherapy consisted of ChlVPP ($n = 9$), ABVD (doxorubicin, vincristine, bleomycin and dacarbazine) ($n = 5$), VEEP ($n = 1$), hybrid ChlVPP/ABVD ($n = 2$) and others ($n = 1$). All 9 patients who received ChlVPP chemotherapy as salvage treatment were initially treated with IF-RT alone.

3.4. *Survival outcome*

Stage ($p = 0.03$) and trial ($p = 0.03$) were significant predictors for survival by univariate analysis. The 10 year OS was 100% for patients in the HD2 trial compared to 86% (95% CI, 72–94%) for patients in the HD1 trial (Fig. 1). The 10 year OS is 97% (95% CI, 78–100%) for stage I patients while for stages II, III and IV it is 89% (95% CI, 75–95%) (Fig. 2). However, on multivariate analysis after adjusting for trial, no variables including age, sex histology or treatment modality were independent significant predictors of survival.

The 10 year DFS according to trial and stage are shown in Figs. 3 and 4, respectively. Once again in multivariate analysis, there were no variables (sex, histology, stage or treatment modality) that were independent of prognostic significance. Ninety-three percent of patients at last followup were alive and disease free. The median followup for both groups was 8 1/2 years.

3.5. *Treatment toxicity*

Late effects were seen in a significant number of patients ($n = 16$) that received IF-RT either as definitive primary treatment or following relapse. The most common late complication was hypothyroidism which was documented in 10 patients (10/24; 42%), all of whom had received IF-RT to the cervical region. Three patients developed muscular wasting of the neck and shoulder areas and each received 35 Gy IF-RT to these regions. A further patient developed scoliosis and hypoplasia of the left chest wall and one patient developed evidence of restrictive lung disease on lung function testing. The latter received six courses of ABVD along with 30 Gy consolidation radiotherapy to the mediastinum following a relapse of HL. One patient developed lymphoedema of the hand after receiving consolidation IF-RT to the axilla following chemotherapy. Data on the fertility status of these patients were not available for analysis. The median age at the time of last followup for the entire cohort for this study was

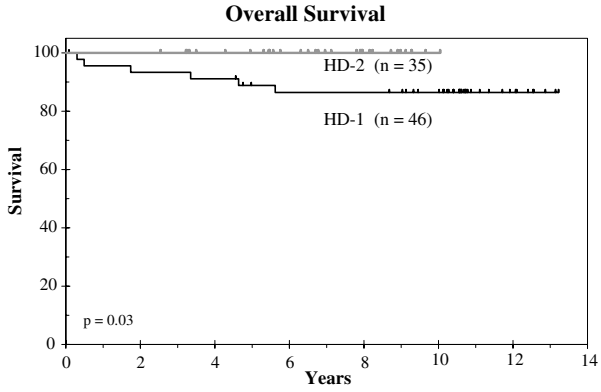

Fig. 1 – Overall survival according to HL trial.

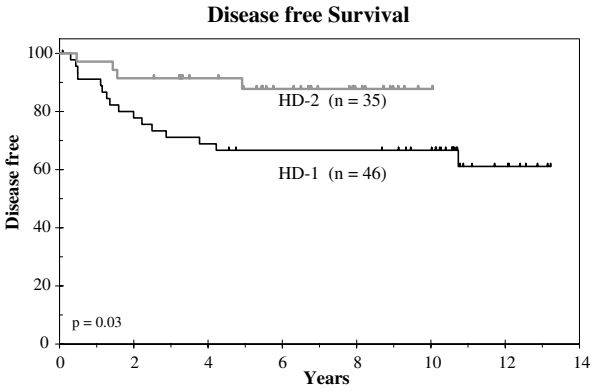

Fig. 3 – Disease free survival according to HL trial.

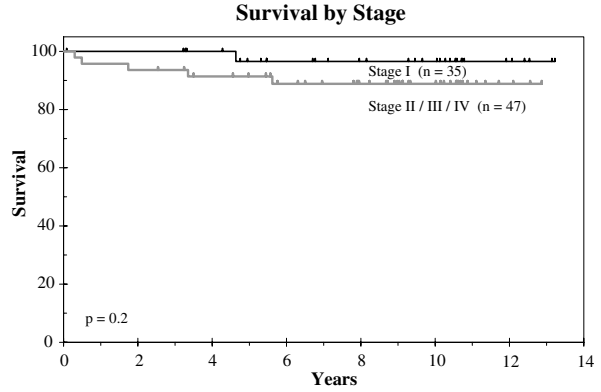

Fig. 2 – Overall survival according to disease stage.

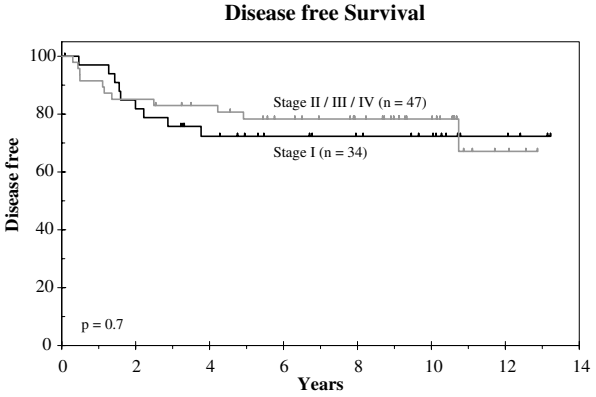

Fig. 4 – Disease free survival according to disease stage.

Table 3 – Causes of death

Stage	Causes of death		
	Disease	Infection	Toxicity
I	–	1	–
II	2	–	–
III	–	1	1
IV	–	–	1
Total	2	2	2

15 years (range, 10–27 years). There have been no second malignant neoplasms to date.

There were six deaths and all were in patients enrolled in the HD1 trial. Two were due to HL (primary progression – 1 or progressive following relapse – 1). The remaining four deaths were due to infection ($n = 2$) and toxicity ($n = 2$). Of the latter four deaths, two were after initial therapy and two occurred following first relapse. One patient developed measles pneumonia during chemotherapy and one died due to overwhelming sepsis. One of the patients who died of chemotherapy-related toxicity was suspected to have an underlying immunodeficiency and died after the first course of ChlVPP chemotherapy (Table 3).

4. Discussion

There are few published reports in the literature of the demographics or natural history of HL in the very young. The incidence rate of 11% in our study correlates well with other previously published reports.[3,8] While NS (44%) and MC (36%) were the most common subtypes of HL, the incidence of LP HL (20%) was comparable with the incidence in older children in both these trials (15%; 99/631). Other published reports have shown a higher incidence of LP subtype in children less than 10 years of age.[9–11] There was a male predominance in our series which is consistent with the published literature[8–10] although Kung and colleagues[3] have reported a significantly higher male predominance with a male:female ratio of 19:1. It is not clear as to why there was such a marked male dominance in the latter study.

In the present study, the initial response rate was excellent with 95% ($n = 77$) of the children achieving CR and this was irrespective of the treatment modality. This superior remission rate is probably a reflection of the high proportion of patients ($n = 66$; 80%) with low stage disease. The only patient who had primary refractory disease had stage IVB disease. Our results are comparable to or exceed other published paediatric HL studies.[8–10] In our cohort, the majority had low stage disease ($n = 66$; 81%) and only two patients had stage IV disease. Furthermore, 20% of our patient cohort had the LP subtype and this subtype of HL is associated with excellent outcome.[12–14] Prognostic factor analysis in children with HL has shown that stage, histology and response to treatment are strong predictors of outcome and it is clear that in this cohort of young patients, these were largely favourable. There were no treatment or toxicity-related deaths in the later HD2 trial. This is likely to reflect better supportive care rather than any treatment-related factor though there was no difference in the recommended supportive care guidance between the two trials.

As is often the case in HL, relapse did not inevitably lead to a poor outcome. Sixteen of the 18, who relapsed after CR, were subsequently salvaged with alternative combination chemotherapy with or without additional RT and in 4 patients with additional high dose chemotherapy with ABMT. This would have been expected as 9 of these patients had only IF-RT as primary therapy and had no previous exposure to chemotherapy. At this time the UK philosophy for the treatment of children with HL was to avoid using combined modality treatment as it was felt that this could result in the worst of both worlds with late toxicities. It therefore chose to explore the use of radiotherapy alone in stage I patients, anticipating that the small proportion who relapse outside the radiation field will be salvaged by chemotherapy. However, the relapse rate among patients who received radiotherapy alone was high (9/24; 38%) in comparison to those (9/53; 17%) who received chemotherapy. Though all nine subsequently attained CR with combination chemotherapy, the total treatment burden was high compared to other childhood HL treatment programmes comprising combined modality treatment. The price of cure has been exacting in the group of patients who relapsed after having received IF-RT for stage I disease. Both of the patients who were in CRu at the end of treatment continue to remain in disease free remission. Clearly, the residual radiological abnormalities at the end of therapy in these 2 patients represented non-viable tumour.

In addition, a significant proportion of patients who received IF-RT ($n = 10/24$; 41%) developed hypothyroidism and soft tissue atrophy, including skeletal growth inhibition ($n = 4$; 17%). These results are similar to those of the Children's Cancer Survivor Study (CCSS) where 34% of all their survivors developed at least one thyroid abnormality.[15] Though very noticeable skeletal and soft tissue dysplasia were seen in only 6 (25%) of the patients who received IF-RT, it is likely that a lesser extent of soft tissue and skeletal abnormalities will have developed in the remaining 18 treated in this manner as the data on soft tissue hypoplasia are underestimated due to the young age of population at followup and by lack of systematic request for such information. To date no patient has developed a secondary malignancy, however, it is not impossible that some of these patients may develop a second cancer in the next decade as the incidence of secondary malignancies is highest in the third decade after completion of treatment.[16–20] In addition, patients treated for head and neck cancers with local radiotherapy are at an increased risk of stroke[21,22], probably due to accelerated atherosclerotic changes within the artery. All these factors underscore the need for proceeding cautiously in the use of IF-RT in young children. The alternative treatment option of using multi-agent chemotherapy regimens containing anthracyclines or procarbazine is equally challenging in the very young. There exists the risk of permanent gonadal damage with the use of alkylating agents such as procarbazine, while anthracycline based regimens may cause life threatening cardiac toxicity. Perhaps, limited combination chemotherapy with low dose IF-RT will be a better therapeutic approach than either

chemotherapy or radiotherapy alone for the very young children with HL.

One of the primary aims of this retrospective study was to evaluate clinical factors that could be identified as prognostic for either DFS or OS. Other than stage at presentation, no factor was predictive for an improved survival outcome. The 10 year OS for stage I patients was 100% compared to 89% for patients with stages II–IV disease. These figures are comparable[3,8,10] or superior to other published reports.[1,23] It is difficult to unravel the precise reasons for the poor outcome in these studies except that some had patients with advanced stage disease and/or a higher incidence of the MC subtype, which historically has been associated with a poorer outcome.[24,25]

These CCLG (Children's Cancer and Leukaemia Group) data contribute to the understanding of the spectrum of disease in this age group and show that very young children with HL have an excellent prognosis. It is concluded that they should be treated with combined modality treatment although to what extent IF-RT can be avoided remains unclear. More recent treatment approaches that omit irradiation on the basis of 18 fluoro-deoxyglucose positron emission tomography based treatment response (FDG PET) may help patient selection.[26–28] Moreover, lymphocyte predominant Hodgkin's lymphoma (LPHL) is now considered as a distinct histopathological entity – a unique form of B cell lymphoma – and contemporary therapeutic regimens used for classical HL are sub-optimal and are unnecessarily aggressive for patients with LP HL. As for childhood HL in general, the focus should be towards maintaining excellent cure rates but limiting and monitoring treatment-related late toxicity.

Conflict of interest statement

No potential conflict of interests for any of the authors.

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