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Clinical outcome in children and adolescents with Hodgkin lymphoma after treatment with chemotherapy alone – The results of the United Kingdom HD3 national cohort trial ☆

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ABSTRACT

Purpose: To assess the efficacy of a standardised hybrid chemotherapy treatment programme for Hodgkin lymphoma (HL) in a national series of children and adolescents.

Patients and methods: The 381 assessable patients, treated between March 2000 and April 2005 in the United Kingdom Children's Cancer Study Group trial, were reviewed to evaluate overall survival (OS), disease free survival (DFS) and deaths. Protocol treatment for stages 2–4 offered a hybrid programme of ChlVbPP (chlorambucil, vinblastine, prednisolone, procarbazine) alternating with ABVcD (doxorubicin, bleomycin, vincristine, dacarbazine). Patients with stage I disease only were offered involved field radiation alone or hybrid chemotherapy.

Results: With a median follow up of 5.1 years (range 0.5–8.4 years), the 5 years OS and DFS for all patients was 97% and 78%, respectively. By multivariate analysis, mediastinal and stage IV disease at presentation were the only factors that affected achieving a complete response. The 5-year DFS rate for patients with stage IV disease was 55% whilst patients with mediastinal disease had a 2-fold higher risk of an event.

Conclusions: This study demonstrated that multi-agent chemotherapy alone is insufficient treatment for patients with mediastinal and stage IV disease.

1. Introduction

The majority of children and adolescents with classical Hodgkin lymphoma (HL) are likely to be cured[1–7] and so current treatment strategies are directed in limiting or avoiding treatment-related adverse effects.[8–11] The Children's Cancer and Leukaemia Group (CCLG – previously known as UKCCSG), chose an alternating hybrid chemotherapy regimen comprising ChlVbPP (chlorambucil, vinblastine, prednisolone, procarbazine) and ABVcD (doxorubicin, vincristine, bleomycin, dacarbazine) as the primary treatment modality for childhood and adolescent HL (United Kingdom HD3 trial). ChlVbPP had been the established protocol in the UK since 1982 whilst ABVbD was widely used in adult practice and as second line treatment in the UK paediatric units. Both regimes were recognised to have long term, dose-dependant toxicities and

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the hybrid regime attempted to minimise these toxicities by reducing the total doses given. Our aim was to evaluate the safety and efficacy of this UK treatment strategy in clinically staged children and adolescents with HL.

2. Patients and methods

2.1. Study design

Children and adolescents up-to their 18th birthday with newly diagnosed, untreated, biopsy proven HL were enrolled onto the HD 2000 02 (HD 3 trial) between March 2000 and April 2005. Disease was staged according to the Ann Arbor system[12] and staging procedures included clinical history, physical examination, chest X-ray, computed tomography or magnetic resonance imaging (neck, chest, abdomen and pelvis) and bone marrow trephine biopsies. There was no requirement for functional imaging with gallium scans for staging. Technetium-99m isotope bone scans were only recommended if the child had specific symptoms of bone pain or had documented stage IV disease at other sites. 18-Fluorodeoxyglucose positron emission tomography (FDG PET) was not a standard investigation in the UK during the period of the HD3 trial. Tumour pathology was centrally reviewed and classified using the Rye criteria.[13] Patients with mediastinal nodal involvement were not sub categorised as bulky or non-bulky mediastinal disease. Residual imaging abnormalities in the mediastinum were not uncommon at the end of treatment and unless there was a high clinical suspicion of residual active disease, such patients were managed expectantly with repeat imaging at 1–3 monthly intervals. Relapse was documented by biopsy but where this was not possible, unequivocal new radiological lesions were accepted as proof of relapse. Ethical approval was obtained and written informed consent was obtained from all patients and/or their parents/guardians according to the then prevailing institutional and ethical committee guidelines.

Table 1 – Characteristics of 381 patients with HL treated with ChlVbPP/ABVcD

Characteristic	No. of patients	%
Age (year)		
<6	26	6.8
6–12	124	32.6
>12	231	60.6
Sex		
Male	235	61.7
Female	146	38.3
Histological subtype		
Lymphocyte predominant HL	47	12.3
Nodular sclerosing HL	255	66.9
Mixed cellularity HL	65	17.1
Lymphocyte deplete HL	0	0.0
HL unspecified	14	3.7
Stage		
I	57	15.0
II	182	47.8
III	70	18.3
IV	72	18.9
Systemic B symptoms		
Yes	162	42.5
No	219	57.5
Mediastinal disease		
Yes	228	59.8
No	153	40.2
Response		
CR (disappearance of evidence of disease)	195	51.2
GPR (reduction of 50% + in any one axis)	146	38.3
PR (reduction of <50% in any one axis)	29	7.6
PD (disease progression of more than 25%)	11	2.9
Treatment		
Involved field radiotherapy	12	3.2
Chemotherapy alone	354	92.9
Chemotherapy plus radiotherapy	15	3.9
Current status		
Alive in CR	301	79.0
Alive after relapse/ progression	62	16.3
Died due to disease	17	4.5
Died of other causes	1	0.2

2.2. Treatment strategy

2.2.1. Chemotherapy

Patients with stage II and stage III disease received three cycles of ChlVbPP/ABVcD chemotherapy whilst those with stage IV disease received four cycles. Each cycle comprised one course each of ChlVbPP and ABVcD. The dosing details of ChlVbPP have been reported elsewhere[1] and both regimes are recorded in Table 2. The interval between the administration of one course of ChlVbPP and the subsequent course of ABVcD was 28 days.

2.2.2. Radiotherapy

Patients with stage I disease who had high cervical disease alone were offered alternatives to their proposed treatment – either involved field radiotherapy (IFRT) alone or two cycles of ChlVbPP/ABVcD chemotherapy. The final choice was at the discretion of local clinician, patient and parent. The radiation dose for those who received IFRT alone was 35 Gy delivered in 20 fractions.

2.2.3. Salvage treatment

Unlike the primary therapy, the salvage treatment strategy consisted of a combination of chemotherapy and radiotherapy. Salvage chemotherapy comprised etoposide, cisplatin, ifosfamide and prednisolone (EPIC) for patients who relapsed after primary treatment with ChlVbPP/ABVcD whilst for those stage I patients who relapsed after IFRT alone were offered two cycles of alternating ChlVbPP and ABVcD. Patients who either achieved a complete response, or a partial response, after two courses of EPIC chemotherapy received involved field radiotherapy (IFRT) to all sites of relapsed disease. Radiation dose at relapse ranged between 25 and 35 Gy and this

Table 2 – Shows the details of chemotherapy ChlVPP/ABVD.

ChlVPP to alternate with ABVD every 28 days	
Chl	Chlorambucil 6 mg/m^2/day PO on days 1–14
V	Vinblastine 6 mg/m^2 (max 10 mg) IV push on day 1 and 8
P	Procarbazine 100 mg/m^2/day PO on days 1–14
P	Prednisolone 40 mg/m^2/day PO on days 1–14
A	Doxorubicin 25 mg/m^2 IV on days 1 and 15
B	Bleomycin 10,000 units/m^2 IV on days 1 and 15
V	Vincristine 1.5 mg/m^2 IV push on days 1 and 15
D	Dacarbazine 375 mg/m^2 IV push on days 1 and 15

Abbreviations: IV – intravenously, PO – orally.
Each cycle alternated every 28 days provided. Platelets > 100×10^9/L and neutrophils > 1.0×10^9/L.

was dependent on organ specific tolerance. High dose therapy (HDT) with subsequent stem cell transplantation (SCT) was a treatment option for patients who had a poor response to two courses of EPIC chemotherapy. All stage IV patients who had a poor response to primary ChlVbPP/ABVcD chemotherapy treatment received IFRT prior to planned HDT and SCT.

2.3. Response criteria

Response assessment in this trial was carried out at the end of treatment and patients grouped into four categories complete response (CR), good partial response (GPR), partial response (PR) and progressive disease (PD). GPR was defined as a reduction of 50% or greater in any one axis of a measurable nodal mass whilst PR was defined as shrinkage of measurable disease that did not achieve a 50% or greater reduction in any one axis. Patients were deemed to have progressive disease if there was an increase in any one axis of a measurable nodal mass (Table 1).

2.4. After treatment follow up

A regular evaluation for detecting asymptomatic relapse and treatment related organ toxicity was undertaken for all patients who completed treatment successfully. Disease related follow-up assessments after completion of treatment included chest X-rays and abdominal ultrasound at four monthly intervals during the first year and at six monthly intervals during the second and third years. Thyroid function tests were performed at six monthly intervals in those who had radiotherapy to the neck while echocardiography was performed at five yearly intervals.

In April 2005 the trial was formally closed as it had exceeded the proposed recruitment targets. Investigators at the treating centres received notification of the closure and management guidelines provided.

2.5. Statistical analysis

The primary end point was disease free survival (DFS) and was measured from date of diagnosis to date of relapse, disease progression or last follow up and analysis was based on an 'intention to treat'. Patients who did not experience any events were censored at their last follow-up visit. Cox regression analysis was used to estimate hazard ratios for comparison between different groups of patients. The secondary end point was overall survival (OS), which was measured from the date of diagnosis to the date of last follow up visit or death. Survival curves were generated by the Kaplan–Meier method[14] and differences were assessed by the log rank statistic.[15] P-values < 0.05 were considered significant. All analysis was based on verified follow up information data as of May 2009. The median follow up for survivors is 5.1 years ranging from 0.5 to 8.4 years.

3. Results

3.1. Patients

Between March 2000 and April 2005, a total of 426 consecutive patients younger than 18 years of age with newly diagnosed HL, including nodular lymphocyte predominant HL, were enrolled in 22 CCLG institutions in the UK and the Republic of Ireland. Of the 426 registered patients, 45 were excluded (central review of histology not consistent with HL ($n = 9$), histology not reviewed centrally (30), major protocol violations ($n = 5$) and age greater than 18 years ($n = 1$)). The demographics, disease characteristics and responses to treatment of the remaining 381 children are shown in Table 1. Age ranged from 2.9 to 17.2 years with a median of 13.2 years. Information on response was missing in 3 patients.

3.2. Protocol deviations

Fourteen patients were switched from ChlVbPP /ABVcD to either six cycles of ABVcD alone or to a predominantly ABVcD chemotherapy regimen (i.e. more cycles of ABVcD than ChlVbPP) due to the nationwide shortage of procarbazine. Though this group of patients did not receive treatment as per protocol, the violations were considered to be minor and all have been included in the final outcome analyses.

3.3. Treatment outcome and response

Of the 381 eligible patients enrolled onto the trial, 366 patients received protocol prescribed therapy: 12 stage IA patients were treated with IFRT alone whilst 354 were treated with combination chemotherapy. Fifteen patients received additional radiotherapy; 14 patients received it as consolidation of their first line treatment while one patient received radiotherapy as part of salvage treatment for progressive refractory disease. Although the use of radiotherapy was a major treatment violation, we have nevertheless decided not to exclude any of these patients for outcome analysis. All 12-stage IA patients who received IFRT alone were in complete remission at the end of radiotherapy. Of the 366 patients (excluding the 15 patients treated with consolidation RT as part of first line therapy) treated with either combination chemotherapy or radiotherapy, 195 patients (51%) were in complete remission at the end of their treatment and 143 patients achieved GPR (37.5%). Patients who achieved only GPR did not receive any additional treatment unless there were unequivocal clinical and or radiological signs of disease progression. On univariate

analysis, children aged 12 years and above, those with advanced stage disease (stages III and IV) as well patients with mediastinal disease had a significantly lower complete remission rates when compared to those who were younger than 6 years of age (odds ratio = 0.4; $p = 0.02$; 95% CI 0.2–0.9), children with early stage disease (odds ratio = 0.6, $p = 0.03$; 95% CI 0.4–1.0) or those patients who had no mediastinal lymphadenopathy (odds ratio = 0.4; $p < 0.002$; 95% CI 0.2–0.7). The presence of B symptoms did not have any impact on response rates. However on multivariate analysis, the presence of mediastinal disease (odds ratio = 0.5; $p < 0.05$; 95% CI 0.3–1.0) and stage IV disease (odds ratio = 0.3; $p < 0.04$, 95% CI 0.1–0.3) were the only factors that affected complete response rates.

3.4. *Survival outcome*

The 5-year OS and DFS rates for the entire cohort of 381 eligible patients were 97% (95% CI 94–98) and 78% (95% CI 74–82), respectively. As 15 patients had also received consolidation radiotherapy as part of their first line treatment, we re-analysed the DFS and OS of the cohort after excluding them. There was no difference in either OS (96%) or DFS (79%) after their exclusion.

The 5-year DFS rate according to disease stage is shown in Fig. 1. The DFS rate was significantly worse for patients with stage IV disease when compared to all other stages (odds ratio = 0.4; $p < 0.001$, 95% CI 0.2–0.6). Multivariate analysis revealed that mediastinal disease was the only predictive factor for DFS; patients with mediastinal disease had a 2-fold higher risk of an event with a trend towards statistical significance (HR = 1.8; $p = 0.06$; 95% CI 1.0–3.4). To date, no event has been observed in any patient after 5 years from study enrolment.

The five-year overall survival (OS) rate for stages I and III was 100%, whilst for stages II and IV it was 95% (95% CI 91–98) and 93% (95% CI 84–97), respectively. There was no statistically significant difference in OS rates between the four stage groups (log rank-test; $p = 0.06$).

The 5-year OS and DFS rates of the 14 patients who received consolidation radiotherapy were 100% and 71%, respectively.

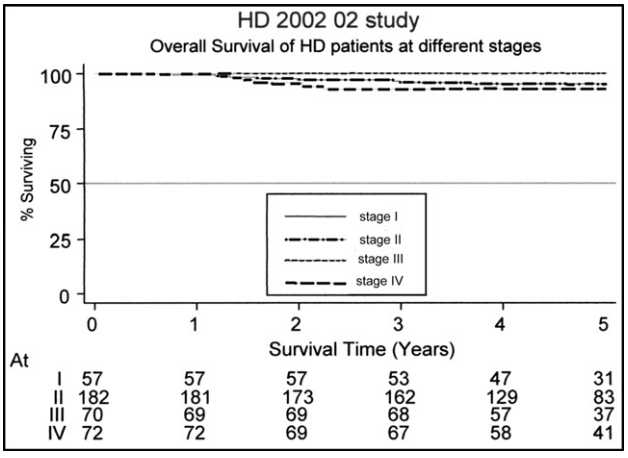

Fig. 1 – Overall survival of HD patients by stage.

In total there have been eighteen deaths to date. Fourteen patients died as a result of disease progression, two patients died due to treatment related complication (sepsis one and graft versus host disease after an allogeneic stem cell transplantation – one). Of the remaining two, one death was secondary to a second malignant neoplasm (rectal adenocarcinoma) while the cause of death for the last patient remains unclear. Table 3 summarises the events and outcome of the entire cohort of patients.

3.5. *Outcome in patients with recurrent and progressive/refractory disease*

3.5.1. *Progressive/refractory disease*

Eleven patients had progressive disease of whom 5 patients had disease progression on initial chemotherapy treatment. The remaining 6 patients had non-responsive disease. Stage distribution in this group was: stage I – 1, stage II – 7 and stage IV – 3. Five have died due to disease progression while six are alive with disease. No factors predictive for refractory disease were identified due to the very small number of patients in this group

3.5.2. *Recurrent disease*

Sixty-seven patients had recurrent disease and majority of the relapses ($n = 41$) occurred within a year of their diagnosis (range, 94 days to 5.0 years). Thirty-seven (55%) of the relapses that occurred in patients only achieved a GPR. Most of the relapses were seen in patients with stage II ($n = 29$) and IV disease ($n = 25$) or those with mediastinal disease ($n = 15$). Only one of the 12 stage IA patients treated with IFRT experienced treatment failure. Nineteen patients have had two or more relapses and nine have died as a result of disease progression.

Seventy-eight patients had either primary refractory disease ($n = 11$) or recurrent disease ($n = 67$) and 24 of these patients were successfully salvaged with second line chemotherapy with and without additional radiotherapy. In addition, 32 children were further consolidated with either an autologous ($n = 29$) or allogeneic stem cell transplantation (AlloSCT) ($n = 3$) as part of their salvage treatment. Two of three who had an AlloSCT had previously received autologous stem cell transplantation and received AlloSCT at second relapse. Twenty-eight of these patients are alive in complete remission while the remaining four died due to progressive disease.

3.5.3. *Toxicity of treatment*

Chemotherapy treatment was well tolerated in the majority and the acute toxicity profile of chemotherapy was comparable

Table 3 – Outcome and events of 381 eligible patients.

Status at last review	
Alive in remission	301
Alive after relapse/progression	62
Deaths	18
Relevant events	
Progression or non-responsive disease	11
Relapsed disease	67
Second primary malignancy	5

with that of other similar chemotherapy regimens used in the treatment of childhood HL. Neutropenia was common but manageable. There were seven serious adverse events reported and these included anaphylactic or allergic reactions ($n = 3$), cardio-respiratory complications ($n = 2$), seizure ($n = 1$) and psychiatric illness ($n = 1$).

3.5.4. *Second malignancies*

There have been five secondary malignancies comprising one case each of follicular carcinoma of the thyroid (FCT), mucinous adenocarcinoma of the colon, diffuse large B cell lymphoma, lymphoproliferative disorder (LPD) and a basal cell carcinoma. The child who developed FCT had received additional involved field radiotherapy (35 Gy/20 fractions) because of presence of persistent disease at the end of treatment. Of the remaining 4 patients, 2 patients had additional chemotherapy for relapsed disease with one patient also receiving autologous stem cell transplantation.

4. Discussion

The primary aim of this study was to evaluate the efficacy of a chemotherapy alone treatment strategy for children and adolescents with HL. The overall 5-year DFS rates reported here are inferior to other published paediatric series where the treatment comprised a multi-modal approach of combination chemotherapy with involved radiotherapy.[3,4,16–18] The DFS of 52% for stage IV is unacceptably low and it appears that the exclusion of involved field radiotherapy (IFRT) has contributed to their poor outcome.

Mediastinal disease at diagnosis was noted to be a poor prognostic factor in our cohort of patients. A likely explanation for this is the observation that a significant proportion of patients with mediastinal disease had residual imaging abnormalities at the end of their treatment. Clearly, residual-imaging abnormalities that were assumed to represent fibrous scar tissue rather than viable tumour were erroneous. This is probably why DFS rates were poorest in patients with stages II and IV (Fig. 1) disease as the presence of mediastinal disease at presentation was highest amongst patients in these groups. Advanced stage and bulky mediastinal disease at presentation have been associated with inferior disease free survival even in children treated with combined modality treatment.[19–21]

The number of children with primary refractory progressive disease ($n = 11/381$; 3%) was relatively high in this study and no factors were identified that were predictive of refractory disease. Contemporary treatment strategies for childhood HL are risk and response adapted and includes positron emission tomography (PET) for both initial staging as well as early treatment response[22,23]

The 5-year overall survival of our cohort is comparable to other published paediatric series which suggests that the salvage rate after relapse is good. This, however, must be balanced with the knowledge that this retrieval has been at the cost of an excessively higher treatment burden for those who had recurrent disease. This is best illustrated by the incidence of second malignancies reported thus far in the study. Within a period of 7 years from the start of this trial, a total of five children have developed a second malignant tumour. A number of studies in childhood and adult cancer have shown that the cumulative toxicity of retrieval therapy contributes appreciably to subsequent risk of a second cancer.[24–27] The use of alkylating agents such as chlorambucil and procarbazine is certainly a contributory factor to the development of a second malignancy in our cohort but more importantly, it is the overall treatment burden that consistently increases the risk, as three of the 5 patients in our series had recurrent disease. Nevertheless, the use of a chemotherapy alone strategy, is not without merit in children with HL as shown in the study by Hakvoort et al. who used a risk adapted chemotherapy alone treatment programme with excellent survival outcomes.[28] Moreover, a treatment strategy using low intensity chemotherapy with cyclophosphamide, vinblastine and prednisolone (CVP) alone has shown to be a safe and effective first line treatment option for patients with early stage nLPHL.[29]

The treatment aim of all childhood and adolescent HL treatment protocols is to minimise toxicity without compromising on efficacy or survival. The overall 5-year survival rate in our cohort provides some support for the use of a chemotherapy alone treatment strategy in newly diagnosed children with good risk HL particularly in the very young so that the long-term effects of radiotherapy can be avoided. Although all stage I patients who were treated with IFRT alone attained a complete remission, the radiation dose administered was relatively high at 35 Gy and it is probable that a combination of chemotherapy and low dose IFRT (15–20 Gy) would be as effective but without the probable late treatment sequelae associated with high radiation doses.

In summary, our study has shown that a single modality treatment strategy using chemotherapy alone is ineffective especially in patients with advanced stage and mediastinal disease. Future attempts at therapy reduction for children and adolescents with HL should be correlated with early treatment response.[30] This is the current approach in the treatment of children classical HL and those with early stage nodular lymphocyte predominant HL where either surgery alone or a short low intensity chemotherapy programme is proposed.[29,31] Continued understanding of the risk and response factors should aim for a reduction in treatment intensity where possible.

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Conflict of interest statement

None declared.

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