Summary report

The 18-30 study

Phase 2 study evaluating the toxicity and efficacy of a modified German Paediatric Hodgkin's lymphoma protocol (HD95) in young adults (aged 18-30 years) with Hodgkin's lymphoma

EudraCT: 2007-003080-45

NCI registry: NCT00666484

Background.

Achieving disease control whilst reducing the long-term side effects of therapy is central to modern therapy of Hodgkin`s lymphoma. The aim of this study is to determine the toxicity and efficacy of a modified German Paediatric Hodgkin's lymphoma protocol (OEPA+COPP chemotherapy followed by modified involved field RT) in patients aged 18-30 yrs with advanced Hodgkin's Lymphoma. (OEPA: Vincristine, Etoposide, Prednisolone, Adriamycin. COPP: Cyclophosphamide, Vincristine, Procarbazine, Prednisolone)

Objectives.

The primary objective was to establish the neurotoxicity of OEPA+COPP chemotherapy in young adults. The secondary objectives were to establish response rates, disease free survival, overall survival and gonadal toxicity.

Methods.

This is a phase II, non-randomised, open-label and single arm trial. Patients were allocated to a treatment group (TG) according to the stage of their disease. Patients in treatment group 1 (TG1, early stages) received two cycles of vincristine, prednisolone, etoposide and adriamycin. Patients in treatment group 2 (TG2, intermediate stages) and group 3 (TG3, advanced stages) received additional two or four cycles of cyclophosphamide, vincristine, procarbazine and prednisolone. Modified involved field radiotherapy ("involved site radiotherapy") was given to sites of initial disease depending on the initial stage of the disease and the response to chemotherapy. Radiotherapy was omitted for TG1 group in complete remission (CR). TG2/3 patients received 20Gy to all previously involved regions if in CR after chemotherapy by CT criteria (PET can be positive or negative). If patients achieved a PR with >75% reduction in all tumour sites by CT (PET scan positive or negative) or patients achieved a PR with 50-75% reduction and negative PET scan, 20Gy was given to all previously involved regions with 30Gy to residual tumours >50ml. If patients achieved a PR with 50-75% reduction but remained PET positive, they received 30Gy to all previously involved regions regardless of size.

Sample size calculations were based on the following assumptions:

- Neurotoxicity rate >15% is unacceptable. If the true neurotoxicity rate is ≤4% treating 45 patients would give a 90% power to exclude a neurotoxicity rate of greater than 15% at the 10% (1-sided) significance level.
- Response rate of <90% is unacceptable. 45 patients would provide 90% power to detect a response rate <80% at the 10% (1-sided) significance level.

Findings.

47 males and females aged 18-30 years with histologically confirmed Hodgkin's lymphoma were recruited to the study. The median follow-up time was 2.6 years. Two patients withdrew from the trial: one withdrew consent before starting trial treatment and the other due to a drug reaction at cycle 1 day 1.

- The rate of any neurotoxicity grade 3 was 8.7% (1 sided 90% CI: 0%-14%); the rate of any neurotoxicity grade 3 and the upper limit of the 90% CI is lower than the unacceptable neurotoxicity rate. Neurotoxicity was largely reversible.
- The overall response rate (CR+GPR+PR) was 100%. The overall response rate is greater than the unacceptable response rate.

The rate of motor, sensory and Ileus/GI toxicity grade 3 was 4.3% (1 sided 90% CI: 0%-8%), 2.2% (1 sided 90% CI: 0%-5%) and 2.2% (1 sided 90% CI: 0%-5%), respectively. Only four patients relapsed, one of whom died due to Hodgkin's disease. None of the 18 patients who achieved CR relapsed or died.

Three cases of avascular necrosis have been reported to date (two grade 2 and one grade 3). Two cases of avascular necrosis were reported as Serious Adverse Events. A further case was detected outside the SAE reporting period during the follow up phase of the trial.

Conclusions.

The neurotoxicity rates and the response rates were both within acceptable limits. Further investigation of this paediatric combined modality regimen in young adults with Hodgkin's Lymphoma appears warranted though steroid related avascular necrosis is a concern.

Table 1 - Baseline patient characteristics

Characteristic	No of patients	%
All patients	47	100
Sex-no (%)		
Female	22	47
Male	25	53
Stage		
II	28	60
III	6	13
IV	13	28
B symptoms		
Absent	25	53
Present	22	47
ECOG performance status		
0	41	87
1	5	11
2	1	2
Extranodal involvement		
Yes (E lesion)	7	15
Yes (Stage IV)	6	13
No	32	68
Not reported	2	4
TG		
TG1 (early stages)	16	36
TG2 (intermediate stages)	11	24
TG3 (advanced stages)	18	40
Compliance		
Non-compliance	2	4

Table 2 - Worst grade of neurotoxicity presented during the trial*

Ever Worst Grade (CTCAE grade criteria)	Motor		Sensory		Ileus/GI		Any neurotoxicity	
	N	%**	N	%**	N	%**	N	%**
1-2	12	26.1	34	73.9	9	19.6	33	71.7
3	2	4.3	1	2.2	1	2.2	4	8.7
Total	14	30.4	35	76.1	10	21.7	37	80.4
2-sided - 95% CI for Grade 3	0%-10%		0%-6%		0%-6%		0.6%-17%	
1-sided - 90% CI for Grade 3	0%-8%		0%-5%		0%-5%		0%-14%	

* Patients who reported neurotoxicity related adverse events are taken into account in the table

** Percentages based on a total of 46 patients (one patient excluded from the analysis because did not start treatment)

Table 3 - Overall response rate

Response	All patients (n=45)		TG1 (n=16)		TG2 (n=11)		TG3 (n=18)	
	No	%	No	%	No	%	No	%
Complete remission	18	40.0	4	25.0	6	54.5	8	44.4
Good partial remission	17	37.8	6	37.5	2	18.2	9	50.0
Partial remission	10	22.2	6	37.5	3	27.3	1	5.6
Overall response (CR+GPR+PR)	45	100.0	16	100.0	11	100.0	18	100.0

*Two patients withdrew from the trial, only 45 completed treatment.

Figure 1-Event free survival (from registration to death or relapse) – Four patients relapsed, one of whom died from Hodgkin's disease

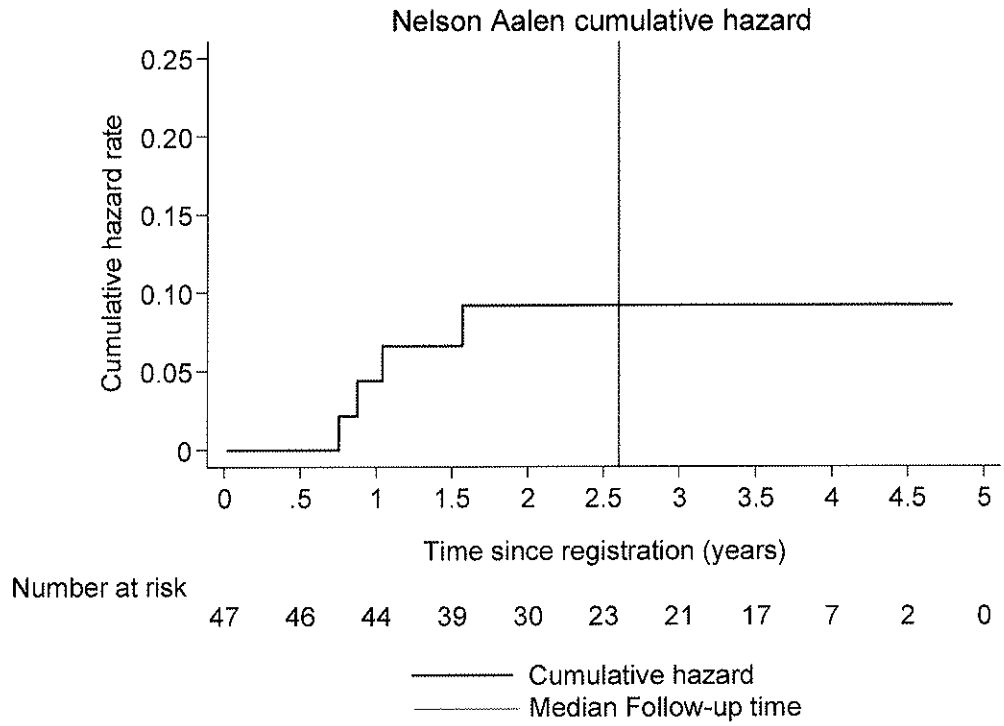

Table 4 - Compliance to chemotherapy by treatment group *

Treatment cycles	TG1 (N=16)	TG2 (N=11)	TG3 (N=18)
OEPA cycle 1	16	11	18
OEPA cycle 2	16	11	18
COPP cycle 1	-	11	18
COPP cycle 2	-	11	18
COPP cycle 3	-	-	18
COPP cycle 4	-	-	18

*Two patients withdrew from the trial and were not allocated to any treatment group. One patient withdrew consent before starting treatment and the other patient withdrew before finishing OEPA cycle 1 due to grade 3 reaction to etoposide

Table 5- Radiotherapy compliance

Radiotherapy compliance	TG1 (N=16)	TG2 (N=11)	TG3 (N=18)	Total (N=45)
Radiotherapy omitted*	4	-	-	4
Radiotherapy given	12	11	18	41
CR after chemotherapy for TG2 and TG3	-	3	7	10
GPR after chemotherapy	8	2	10	20
PR after chemotherapy	4	6	1	11

*Therapy omitted for patients in TG1 who achieved CR after chemotherapy by CT (>95% reduction in tumours and <2ml residuals) and PET criteria

Table 6 - The worst toxicity grade at any point in time of the trial (excluding neurotoxicity)

Toxicities (CTCAE grade criteria)	Grades 1-2 Number of patients	(%)**	Grades 3-4 Number of patients	(%)**
HAEMATOLOGICAL				
Blood/bone marrow				
Neutrophils	3	7	35	76
Platelets	6	13	4	9
Haemoglobin	4	9	0	0
NON-HAEMATOLOGICAL				
Gastrointestinal				
Nausea	21	46	3	7
Vomiting	12	26	3	7
Diarrhoea	11	24	2	4
Mucositis/stomatitis	15	33	5	11
Heartburn/dyspepsia	5	11	0	0
Anorexia	1	2	0	0
Constipation	5	11	1	2
Dental: teeth	1	2	0	0
Distention/bloating, abdominal	2	4	0	0
Taste alteration (dysgeusia)	1	2	0	0
Gastritis	1	2	0	0
Haemorrhage/bleeding				
Haemorrhage - GU - Bladder	4	9	0	0
Pulmonary/upper respiratory - Nose	1	2	0	0
Dermatology/skin				
Alopecia	32	70	-	-
Rash	7	15	0	0
Pruritis	3	7	0	0
Rash: hand-foot skin reaction	1	2	0	0
Constitutional symptoms				
Insomnia	10	22	1	2
Fever	7	15	2	4
Rigors/Chills	2	4	0	0
Fatigue	33	72	1	2
Sweating (diaphoresis)	3	7	0	0
Weight loss	1	2	0	0
Pain				
Neurological-headache	12	26	0	0
Muscoloskeletal - muscle	15	33	1	2
Muscoloskeletal - bone	8	17	1	2
Gastrointestinal - abdomen NOS	3	7	2	4
Pain NOS	1	2	0	0
Musculoskeletal - neck	1	2	0	0
Musculoskeletal - back	4	9	2	4
Musculoskeletal - extremity - limb	5	11	0	0
Musculoskeletal - joint	1	2	1	2
Pulmonary/upper respiratory - chest/thorax NOS	1	2	0	0
Gastrointestinal - esophagus	4	9	0	0
Gastrointestinal - dental/teeth/periodontal	3	7	0	0
Renal/genitourinary - bladder	1	2	0	0
Cardiac				
Cardiac NOS	2	4	0	0
Hypotension	2	4	2	4

Table 6 - The worst toxicity grade at any point in time of the trial (excluding neurotoxicity)

Toxicities (CTCAE grade criteria)	Grades			
	1-2		3-4	
	Number of patients	(%)**	Number of patients	(%)**
Infection				
Infection with unknown ANC	12	26	9	20
Neurology				
Mood alteration NOS	11	24	0	0
Dizziness	2	4	0	0
Mood alteration - anxiety	1	2	0	0
Memory impairment	1	2	0	0
Musculoskeletal/soft tissue				
Muscle weakness	3	7	0	0
Osteonecrosis (avascular necrosis)	1	2	0	0
Lymphatics				
Edema - limb	1	2	0	0
Pulmonary/Upper respiratory				
Cough	6	13	0	0
Dyspnea	1	2	0	0
Ocular/visual				
Vision - blurred vision	1	2	0	0
Ocular/visual - other ('visual disturbance')	1	2	0	0
Sexual/reproductive function				
Erectile dysfunction	1	2	0	0
Irregular menses	2	4	0	0
Endocrine				
Hot flashes/flushes	2	4	0	0
Allergy/Immunology				
Rhinitis	1	2	0	0
Metabolic/laboratory				
ALT	1	2	0	0
Metabolic/laboratory - other (Gamma GT elevated)	1	2	0	0
Metabolic/laboratory - other (urea elevated)	1	2	0	0
Vascular				
Thrombosis/embolism (vascular access-related)	0	0	1	2
Thrombosis/thrombus/embolism	0	0	1	2

* 29 patients presented grade 4 neutropenia at any point of the trial

§ 1 patient presented grade 4 aching muscles and joints

‡ 1 patient presented grade 4 hypotension

** Percentages based on a total of 46 patients (one patient excluded from the analysis because did not start treatment)

Table 7 - The worst SAE grade and number of SAE reported

CTCAE grade criteria	Grades				Number of SAE
	1-2		3-4		
	Number of patients	(%) §	Number of patients	(%) §	
Blood/bone marrow					
Neutrophils*	0	0	10	22	11
Heamoglobin	1	2	0	0	1
Gastrointestinal					
Diarrhoea	4	9	1	2	5
Constipation	2	4	0	0	3
Dehydration	1	2	0	0	1
Mucositis/stomatitis	0	0	3	7	3
Nausea	0	0	2	4	2
Vomiting	0	0	3	7	3
Ascites	0	0	1	2	1
Pain					
Gastrointestinal - abdomen NOS	0	0	3	7	3
Musculoskeletal - back	1	2	0	0	1
Musculoskeletal - bone	0	0	2	4	2
Pain NOS	0	0	1	2	1
Musculoskeletal - extremity - limb	0	0	1	2	1
Musculoskeletal - joint	2	4	1	2	4
Musculoskeletal/soft tissue					
Osteonecrosis	1	2	1	2	3
Infection					
Colitis infectious	0	0	1	2	3
Infection with unknown ANC	0	0	7	15	7
Neurology					
Neuropathy sensory	1	2	1	2	2
Neuropathy motor	0	0	1	2	1
Neurology – brain (encephalitis)	1	2	0	0	1
Constitutional symptoms					
Fever	5	11	0	0	5
Ocular/visual					
Opthalmoplegia	1	2	0	0	1
Vascular					
Hypotension**	0	0	1	2	1
Thrombosis/thrombus/embolism	1	2	1	2	3
Pulmonary/upper respiratory					
Pleural effusion	0	0	1	2	1

* Six patients presented grade 4

** Patient presented grade 4

§ Percentages based on a total of 46 patients (one patient excluded from the analysis because did not start treatment)

Table 8 - Worst grade of radiotherapy toxicity reported 6 months after the end of radiotherapy

Worst grade reported of radiotherapy toxicity (RTGO criteria)	Patients who received radiotherapy (N=41)						Total (%)
	Mild		Moderate		Severe		
	N	%	N	%	N	%	
Skin problems §	3	7.3	2	4.9	0	0	5 (12.2%)
Mucositis ∫	8	19.5	2	4.9	2	4.9	12 (29.3%)
Gastrointestinal ‡	5	12.2	2	4.9	0	0	7 (17.1%)
Other acute toxicity*	10	24.4	2	4.9	2	4.9	14 (34.2%)
Any radiotherapy toxicity	16	39	4	9.8	3	7.3	23 (56.1%)

§ Skin problems: 2 patients with moderate Erythema

∫ Mucositis: 1 patient with moderate oral mucositis, 1 patient with moderate mouth mucositis, 1 patient with severe throat and mouth mucositis, 1 patient with severe mouth and oesophagus mucositis

‡ Gastrointestinal: 1 patient with moderate Nausea, 1 patient with moderate Diarrhoea)

* Other acute toxicity: 1 patient with moderate Anorexia, 1 patient with moderate abnormal taste perception; 1 patient with severe Frontal headache, 1 patient with severe dysphagia