EuroNet-PHL-C1

EuroNet-Paediatric Hodgkin's Lymphoma Group

First international Inter-Group Study for classical Hodgkin's Lymphoma in Children and Adolescents

- No radiotherapy in patients with adequate response at first restaging after two cycles of chemotherapy
- Randomised comparison of Procarbazine versus Dacarbazine (within COPP versus COPDAC) in patients in intermediate and advanced stages
- Standardised risk- and response-adapted salvage strategy

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Inter-group chairpersons

Prof. Dr. Dieter Körholz

(Coordinating investigator)

Zentrum für Kinderheilkunde
Universitätsklinik und
Poliklinik für Kinder- und
Jugendmedizin
Ernst-Grube-Straße 40,
06120 Halle (Saale)
Germany

Dr. W. Hamish Wallace

Royal Hospital for Sick Children,

Sciennes Road, Edinburgh EH9 1LF,

Scotland, UK.

Prof. Dr. Judith Landman-Parker

Service d'hématologie et d'oncologie pédiatrique

Hôpital Trousseau AP-HP
Paris France

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	+ 2nd amendment (dated 05.12.2007)

1.1 PROTOCOL SYNOPSIS

Title of the study	First international Inter-Group Study for classical Hodgkin`s Lymphoma in Children and Adolescents
Acronym	EuroNet-PHL-C1
Sponsor	University of Halle/Wittenberg
Indication	Classic Hodgkin's lymphoma in childhood and adolescence – first and second line treatment
Objective	Building on the experience of the GPOH-HD study group since 1978, first and second line therapy for childhood Hodgkin's lymphoma shall be further optimised to avoid over-treatment and decrease long-term complications. ▪ FDG-PET currently is routinely used in most centres. Results of FDG-PET are now formally integrated both into staging and response assessment. ▪ In all treatment groups, radiotherapy after completion of chemotherapy will be omitted in patients with adequate response (CR or PR with negative PET) after two cycles of OEPA. ▪ In intermediate and advanced stages (TG-2 & TG-3), COPDAC chemotherapy (replacing Procarbazine by Dacarbazine in order to reduce risk of infertility) is randomised versus standard COPP. ▪ Relapse treatment is standardised for three relapse groups based on time to failure and initial treatment group.
Primary objectives	1. Are 5 year event free survival (EFS) rate estimates in patients with adequate response after 2 OEPA treated without radio-therapy consistent with a target EFS rate of 90% in all treatment groups? 2. Can Procarbazine be safely replaced by Dacarbazine in therapy groups TG-2 and TG-3 without a deterioration of EFS (randomised comparison of COPDAC and COPP)? 3. Description of treatment outcome to a standardised risk adapted relapse strategy

Secondary objectives	1. Is the 5 year event free survival (EFS) rate in patients with inadequate response after 2 OEPA who receive standard involved field radiotherapy consistent with a target EFS rate of 90% estimates in all treatment groups? 2. Does substitution of Dacarbazine for Procarbazine in TG-2 and -3 patients decrease the rate of infertility in males and premature menopause for females?
Tertiary objective	Exploration of the impact of real-time central staging and response assessment on treatment outcome.
Study design	• Quality control treatment titration study in a stable patient population addressing consistency of absolute 5-year EFS rate estimates with a target rate of 90%. • Embedded randomised controlled chemotherapy comparison in TG-2 and TG-3 concerning efficacy and toxicity. • Quality control treatment titration study for standardised risk adapted relapse therapy. In two subgroups, “patients with late relapses after TG-1” and “adequately responding patients with early relapse or late relapse after TG-2 or TG-3” consistency of absolute 5-year EFS rate estimates with a target rate of 90% is addressed.
Study population	• Patients with untreated classical Hodgkin’s lymphoma under 18 years of age. (In France only above one year.) and • Patients with 1st relapse of Hodgkin’s lymphoma after EuroNet-PHL-C1 first line treatment or after treatment according to or comparable to previous GPOH/DAL studies.
Sample size	At least 1200 patients with real time central review will be included in the study on primary therapy. In addition about 600 patients of the SFCE, the PPLLSG and further national study groups using local staging and response assessment are expected. According to past experience these patients are distributed among the therapy groups 1 or 2 and 3 in a ratio of 36:28:36. For the relapse study at least 150-250 patients are expected.
Therapy	All first line patients get two cycles of OEPA and then undergo response assessment including FDG-PET. Patients in TG-1 do not receive further chemotherapy. Patients in TG-2 and -3 are randomised to receive either COPP or COPDAC for two or four cycles respectively. If an adequate response was documented

	treatment stops after chemotherapy. In case of inadequate response to 2 OEPA involved field radiotherapy follows for all treatment groups. Relapse patients get therapy adapted to risk and response (details cp. chapter 9).
Primary end point	Event free survival (EFS) defined as time from registration until the first of the following events: • progression/relapse of disease • diagnosis of a secondary malignancy • death of any cause.
Secondary end points	1. Overall survival (OS) 2. Progression free survival (PFS) 3. CTC (Common toxicity criteria) toxicity levels of therapy elements 4. Evidence of male infertility score / Female sexual functioning score 5. Long-term consequences (premature menopauses, secondary cancer etc.)
Biometry	• 5-year EFS rates for TG-1 and TG-2 & -3 will be estimated (with 95% confidence intervals) in patients with adequate response after 2 OEPA (and secondarily also in patients with inadequate response). Precision (i.e. halve width of the 95% confidence interval) is expected to be ± 5-6%. The target rate is set at 90%. • In TG-2 and TG-3 COPP is randomly compared to COPDAC. The log hazard ratio will be estimated along with a 95% confidence interval within a proportional hazard model including the factors treatment group (TG-2 versus TG-3), central versus local staging and response assessment and therapy (COPP versus COP-DAC). Differences in (particularly gonadal) toxicity will be compared. • In the relapse study 5-year EFS rates are described in defined subgroups.
Schedule	The study started in Germany on 30.01.2007. For insurance reasons the study accrual in Germany is limited to less than 5 years and an individual follow-up of up to 5 years. Other countries join the study as soon as possible. Overall accrual stops on 29.01.2013. Individual follow-up for 5 years after study entry is required for this

	protocol. Long-term follow-up is strongly recommended and will be organised according to national circumstances.
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