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ORIGINAL ARTICLE

Hodgkin lymphoma – a survey of children and adolescents treated in Sweden 1985–2009

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ABSTRACT

Background. Hodgkin lymphoma (HL) in children constitutes approximately 30% of all pediatric lymphomas in Sweden. The chance of cure is high, but the frequency of late effects has been considerable. Over recent years, efforts have been made to reduce treatment with maintained survival.
Material and methods. All patients 0–17 years, identified in the Swedish Childhood Cancer Register as diagnosed between 1985 and 2009, were included. The material was analyzed using descriptive statistics and for survival estimates the Kaplan-Meier method was used.
Results. Three hundred and thirty-four patients were identified during this time period. The median age was 14 years. Male sex was over-represented, especially in lower age groups and in nodular lymphocyte predominant Hodgkin lymphoma (NLPHL). In nodular sclerosis and in age group 15–17 years, female sex dominated. Most of the cases presented in stages I or II. B-symptoms were present in 38% of cHL, but only in 7% of NLPHL. The number of patients receiving radiotherapy has been significantly reduced during the period studied. The relapse rate in cHL was $10 \pm 2\%$ and in NLPHL $16 \pm 7\%$. The relapse rate was significantly higher in cHL stage IIB compared to other stages in the same therapy group. In cHL 6% died, and in NLPHL 0%. The 5-, 10- and 20-year overall survival estimates in cHL were $96 \pm 1\%$, $95 \pm 1\%$ and $90 \pm 3\%$, respectively, with no significant difference when comparing different treatment regimens and time periods. The 5- and 10-year overall survival after relapse in cHL was $81 \pm 8\%$ and $75 \pm 10\%$, respectively.
Conclusion. During the period studied there is no indication of a decline in survival despite changes in treatment. Survival rates in Sweden are high, and even after relapse chances of cure are high. We were not able to identify any characteristics specific for the group of patients that did not survive.

Hodgkin lymphoma (HL) in children is rare, with an incidence of 0.5/100 000 [1] for children 0–14 years of age in Sweden, compared to 2/100 000 [2] in adults. This represents about 30% of all lymphomas in children and 5–10% of all lymphomas in adults. For many years, the survival rates have been high in the industrialized world. However, the rate of severe late effects is considerable. The main late effects of treatment are secondary malignancies [3, 4], cardio-pulmonary diseases [5, 6] (lung fibrosis, pneumoni-tis, cardiac failure, and arteriosclerosis), muscular atrophies [7], infertility [8], hypothyroidism and growth retardation [9]. In order to reduce the early and late effects the treatment protocols have been constantly evaluated and altered over recent decades, to reduce radiotherapy and to use less toxic chemo-therapy [10, 11].

The Swedish Childhood Cancer Register, initi-ated in the early 1980s, provides a unique opportu-nity to learn more about HL in Swedish children. The aim of this study of pediatric HL was to investigate incidence, age, sex, subgroups, stage, treatment, relapse, survival and whether there are any indications that the changes in treatment has resulted in a decline in overall survival (OS) or event-free survival (EFS). Another aim was to iden-tify characteristics specific for the group of patients who did not survive.

Material and methods

Material

All patients 0–17 years at diagnosis, identified in the Swedish Childhood Cancer Register as diagnosed with HL between 1985 and 2009 were included in this register study.

The Swedish Childhood Cancer Register comprises patients up to 18 years of age at time of diagnosis. The register was ethically approved by all the different regional ethics review committees in Sweden headed by the Karolinska Institutet ethics review committee; KI Dnr 03–642. Informed consent to register data was obtained from parents. Some teenagers with HL, 15–17 years old, may, especially during the first part of the study period, have been treated in adult oncology clinics and may not have been reported to the Swedish Childhood Cancer Register. However, a cross check with the Swedish Cancer register did not indicate that this was a significant problem. In this article we present data for the whole group of 0–17-year-olds, but in addition to this we also present data for the group of 0–14-year-olds to allow comparison with many other reports on cancer in children where this definition is used.

Patient charts from the deceased patients have been studied in more detail to identify characteristics specific for this group.

Classification and staging. The WHO classification of HL [12] is based on morphological findings and divided into different groups: classical Hodgkin lymphoma (cHL) and nodular lymphocyte predominant HL (NLPHL), which is a subclass of HL with somewhat different morphology and biology. NLPHL has been reported in about 5% of adult HL [13], but more commonly in adolescents and children [14]. Results for NLPHL will be reported separately. cHL is further divided into four subgroups: lymphocyte rich classical HL (LRcHL), nodular sclerosis (NScHL), mixed cellularity (MCcHL) and lymphocyte depleted HL (LDcHL). Biopsy material from 71 patients (the Uppsala-Stockholm region) has been re-evaluated by an experienced lymphoma specialized pathologist resulting in exclusion of one patient where the re-evaluation showed NHL instead of HL. The staging system used is Cotswold's modified version of the Ann Arbor's classification [15].

Treatment. There are six regional pediatric oncology centers in Sweden. Since the formation of the Swedish Childhood Solid Tumor Working Group (VSTB) in 1983 the consensus has been that the different tumors should be uniformly treated in all Swedish children and that the treatment should be delivered at, or at least directed from, a pediatric oncology center. Radiotherapy has only been given at these centers. Before 1996, most patients received chemotherapy consisting of MOPP (mechloretamine, vincristine, procarbazine, prednisone) or MOPP/ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine), together with or without radiotherapy, while a few were treated only with surgery or radiotherapy. Since 1996, all Swedish children with HL have been treated according to the protocols in clinical trials organized by the German Pediatric Oncology & Hematology Group (GPOH) and from 2006 by the European Euro-Net Pediatric Hodgkin's Lymphoma Group and a great majority included in the studies whenever they have been open and the patients/families have agreed to participate. In these protocols, the patients have been divided into therapy groups (TG) as follows: TG 1: Stage I A/B and II A, TG 2: Stage I_E A/B, II_E A, II B and III A, and TG3: Stage II_E B, III_E A/B, III B and IV A/B. Since 1996 different combinations of OPPA/OEPA (vincristine, prednisone, procarbazine vs. etoposide, doxorubicine)/COPP (cyclophosphamide, vincristine, prednisone, procarbazine) have been used, and since 2006 OEPA/COPP/COPDAC (procarbazine replaced by dacarbazine) has been used according to the protocols of the different clinical trials (GPOH-HD 95, GPOH-HD 2002 pilot, GPOH Interim, and EuroNet-PHL-C1). The doses of radiotherapy have gradually been reduced, and in some groups omitted, depending on response to therapy measured by volume- and/or FDG-PET (fluoro-deoxy-glucose positron emission tomography) uptake reduction. An overview of the different treatment strategies is presented in Table I.

Methods

Descriptive statistics was used for incidence, age, sex, subgroups, stage and treatment. The χ^2-test was used for comparison between groups and the Kaplan-Meier method was used for survival estimates. OS and EFS was studied in relation to sex, age at diagnosis, therapy groups, stage, protocols, B-symptoms and subgroups of HL. To investigate whether there was a change in OS and EFS after changes in therapy in 1996 and onwards, the patients were divided in two groups. Those receiving therapy according to protocols from the middle of the 1990s, initiated by GPOH and later the EuroNet-PHL-C1 study, were compared to those treated earlier. It must be emphasized that the power to detect small changes in survival is very limited in a small study like ours, and therefore especially when no difference has been detected the results must be interpreted with caution and equivalence cannot be assumed. Similarly, when performing sub-group analyses, this problem is even more pronounced. OS is an estimation of the proportion of

Table I. Overview of the different treatment protocols. 1985–1996: MOPP or MOPP/ABVD 4–8 cycles followed by RT involved field (IF) 25–40 Gy or extended field (EF) (mantle field, inverted Y-field or total nodal irradiation) up to 40 Gy depending on stage and response to therapy. 1996–2009:

Protocol:	TG-1:	TG-2:	TG-3:
GPOH HD-95	F: 2 × OPPA M: 2 × OEPA RT: CR: no RT Non-CR: 20 Gy IF + boost remaining tumor max 35 Gy	F: 2 × OPPA, 2 × COPP M: 2 × OEPA, 2 × COPP RT: See TG-1	F: 2 × OPPA, 4 × COPP M: 2 × OEPA, 4 × COPP RT: See TG-1
GPOH- HD 2002 pilot	F: 2 × OPPA M: 2 × OE*PA RT: See GPOH-95 TG-1	F: 2 × OPPA, 2 × COPP M: 2 × OE*PA, 2 × COPDAC RT: All 20 Gy IF + boost remaining tumor max 35 Gy	F: 2 × OPPA, 2 × COPP M: 2 × OE*PA, 2 × COPDAC RT: See GPOH-HD 2002 pilot TG-2
EuroNet-PHL-C1	M/F: 2 × OE*PA RT: CR or non-CR PET neg: no RT. Others: 20 Gy IF + boost remaining tumor max 30 Gy	M/F: 2 × OE*PA, 2 × COPP or COPDAC. RT: See EuroNet-PHL-C1 TG-1	M/F: 2 × OE*PA, 4 × COPP or COPDAC. RT: See EuroNet-PHL-C1 TG-1

EF, extended field, IF, involved field, RT, radiotherapy, *25% more etoposide.
COPDAC, procarbazine in COPP is replaced by dacarbazine iv 250 mg/m^2 day 1–3.
COPP, cyclophosphamide 500 mg/m^2 day 1, 8; vincristine 1.5 mg/m^2 day 1, 8; prednisone 40 mg/m^2 day 1–15, procarbazine 100 mg/m^2 po day 1–15.
MOPP/ABVD, mechloretamine 6 mg/m^2 day 1, 8; vincristine 1.5 mg/m^2 day 1, 8; procarbazine hydrochloride 100 mg/m^2 day 1–14, prednisone 40 mg/m^2 day 1–14.
Doxorubicin 25 mg/m^2 iv day 29, 44, bleomycin 10 mg/m^2 day 29, 44, vinblastine 6 day 29, 44, dacarbazine 375 mg/m^2 day 29, 44.
OEPA, vincristine 1.5 mg/m^2 day 1, 8, 15; etoposide 125 mg/m^2 day 1–4 (-5 in OE*PA); prednisone 60 mg/m^2 day 1–15, doxorubicin 40 mg/m^2 day 1, 15OPPA, vincristine 1.5 mg/m^2 day 1, 8, 15; procarbazine 100 mg/m^2 day 1–15; prednisone 60 mg/m^2 day 1–15, doxorubicin 40 mg/m^2 day 1, 15.

children that will survive. In this analysis, induction death, death in remission or death following relapse are defined as events. EFS is an estimation of the final proportion of children in complete remission (CR) compared to all children in the study group. In this analysis, relapse, secondary malignancy or death due to any cause are defined as events. With long follow-up time, the p-EFS will approach the percentage of children in CR. The log-rank test was used as the significance test when comparing survival in different groups. An additional analysis of the effect of different co-variates on OS and EFS was made using Cox regression analysis. The level of significance was set at 0.05. The statistical analyses were performed using SPSS 18.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results

Incidence, age and sex (all subgroups)

Between 1 January 1985 and 31 December 2009, 335 children under 18 years of age were diagnosed with HL in Sweden and registered in the Swedish Childhood Cancer Register. One was excluded after re-evaluation of the diagnosis. Of the 334 children, 200 were < 15 years of age at diagnosis and the youngest child was diagnosed at the age of two.

The overall annual incidence in the age group 0–14 years was 0.5/100 000 Swedish children with a male predominance (M/F ratio = 1.65 corrected for the natural sex distribution in the population) and increasing incidence with age. The incidence in the 0–17-year-old group was 0.7/100 000 and the sex distribution was M/F ratio = 1.22. No change in incidence trend was observed over these 25 years (Figure 1). The median age at time of diagnosis was 14 years of age. Boys predominated in the younger age groups, especially in the group 0–4 years of age in which all 11 cases were boys, but in the group 15–17-year-olds there was a slight preponderance of girls (55%) (Figure 2).

Histological subgroups

The distribution of subgroups was NScHL 68% (n = 227), MCcHL 15% (n = 50), NLPHL 13% (n = 42), LDcHL (n = 4) 1%, no case of LRcHL,
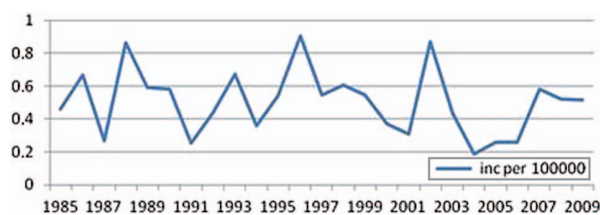

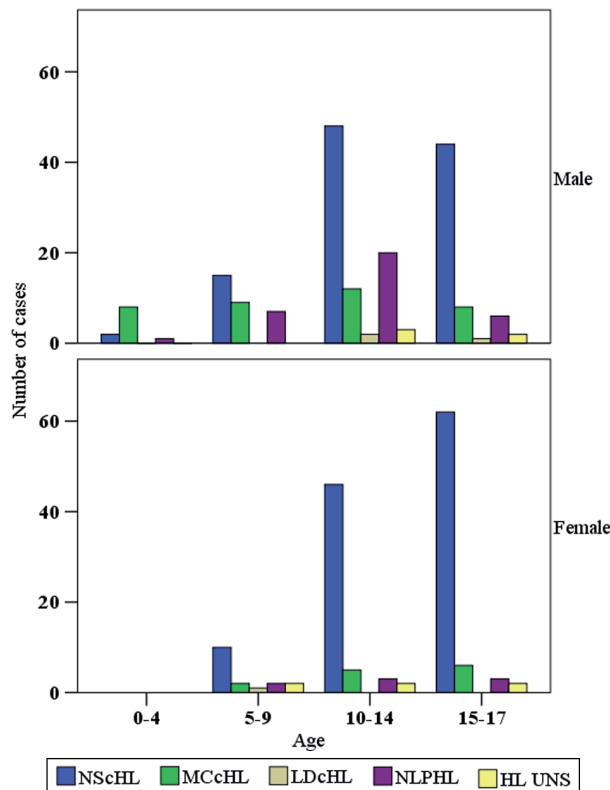Figure 1. Incidence per 100 000 children, 0–14 years 1985–2009, all subgroups, in Sweden.

Figure 2. Distribution of subgroups in different ages, male and female, respectively.

and unspecified HL 3% (n = 11). The distribution in different age groups is shown in Figure 2. For NScHL, a slight female predominance (52%) was found, while the other subgroups were more common among boys (74–81%). NScHL is the most dominant subgroup among 15–17 year olds (79%), and contributed to 18% of the cases in 0–4 year olds. In MCcHL 73% of the cases occurred among the youngest and 10% in the 15–17-year-old age group. NLPHL will from now on be reported separately.

Classical HL

The total number of patients with cHL was 292. The median age was 14 (2–17). The sex distribution was 53% boys and 47% girls.

Stage. Most of the cases presented in early stages; stage I 10% (n = 30), II 60% (n = 174), III 19% (n = 55), IV 11% (n = 31). In two cases, information about stage was missing. B-symptoms were reported in 38% of the cases and were more common in higher stages, especially in MCcHL where 80% had B-symptoms in stage IV. All cases (n = 4) with LDcHL presented with B-symptoms. Higher stages (stage III and IV) were more common in the last period, 36%, versus 19% in the earlier period.

Treatment. One hundred patients were treated with MOPP or MOPP/ABVD, together with or without radiotherapy. One hundred and seventy-two patients received treatment according to the GPOH protocols or the EuroNet-PHL-C1 protocol. Seven patients received only radiotherapy (NScHL stage IA or IIA). In the case of 13 patients, the treatment was not known. At least 69% (n = 202, 15 missing data) of the patients received radiotherapy in the first-line treatment. Patients treated according to EuroNet-PHL-C1 received radiotherapy significantly less often compared with patients treated according to the GPOH protocols and older treatments 42% versus 76% versus 76% (p = 0.002). When comparing treatment before and after 1996, the corresponding figures are 79% versus 65% (p = 0.08).

Survival analyses. The 5-, 10- and 20-year OS estimates (all cHL patients) were 96 ± 1%, 95 ± 1% and 90 ± 3%, respectively, with a mean follow-up time of 11.4 (0–25.5) years. There was no significant difference in OS between boys and girls, different age groups, those with or without B-symptoms or different groups of treatment. Children treated before 1996 (group 1, n = 107) had a mean follow-up time of 18 (0.5–25.5) years and 11 patients had died, 0.5–17 years after diagnosis. Children treated after 1996 (group 2, n = 172) had a mean follow-up time of 7.1 (0–14.5) years and seven of the patients had died, 0–2.9 years after date of diagnosis. When comparing treatment, 13 patients were not included in either group due to lack of information. The 5- and 10-year OS was 97 ± 2% and 94 ± 2%, respectively, in group 1, and 96 ± 2% and 96 ± 2% in group 2 (Figure 3). The 5- and 10-year EFS were 88 ± 2% and 87 ± 2%, respectively. There were no significant differences between the groups (group 1 89 ± 3% and 88 ± 3%, group 2 88 ± 3% and 86 ± 3%) (Figure 4). Neither were there any significant differences in EFS when comparing the three therapy groups. In TG 2, stage IIB had significantly lower EFS compared with the other stages in the same group (stage IIAE, IIIA) (p = 0.028) (Figure 5). This pattern was seen both in patients treated before 1996 and after, although it was statistically significant only for the whole group and for the group treated after 1996. With cox regression analysis, including the co-variates: year of diagnosis, age, sex, stage, B-symptoms and group of treatment (before vs. after 1996), patients with B-symptoms had marginally significant lower EFS (p = 0.05).

Relapse. Twenty-nine of the 292 children with cHL relapsed (10%) with a relapse rate of 10 ± 2%. The mean and median time from diagnosis to relapse was 1.6 and 1.0 years, respectively, (0.4–6.5 years). They
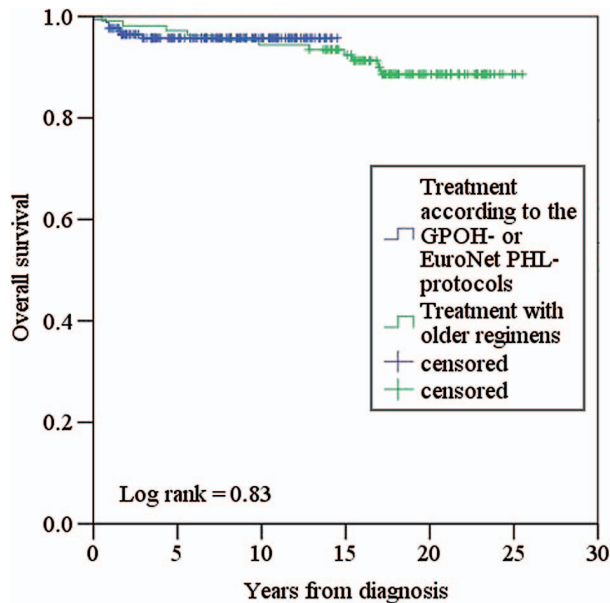
Figure 3. Overall survival cHL, different treatment strategies compared (before and after 1996 respectively).

Figure 5. EFS, stages in TG2 compared.

had a median age of 14 years of age (3–17 years) at time of primary diagnosis of HL and there was a tendency towards male predominance (M/F ratio = 2.1, p = 0.065). The distribution of the different subgroups was: NScHL 25/227 (11%), MCcHL 3/50 (6%) and LDcHL 1/4 (25%) (Table II).

The number/proportion in each stage was one in stage I (3% of all stage I patients), 20 in stage II (11% of all stage II patients), three in stage III (6% of all stage III patients) and five in stage IV (16% of all stage IV patients). B-symptoms at
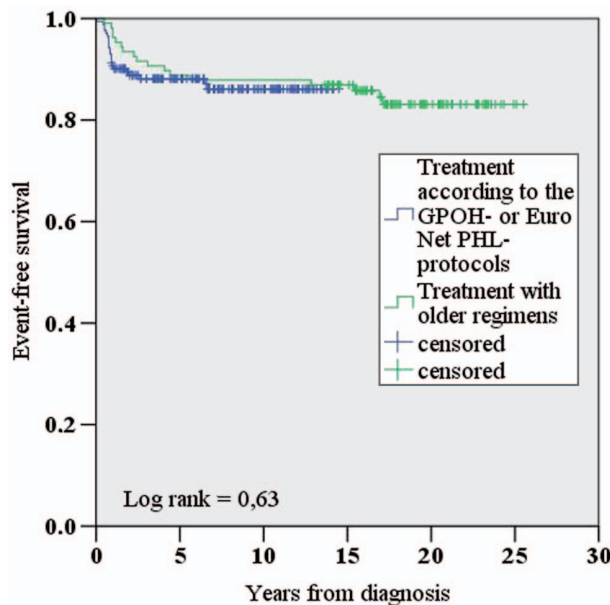
presentation were found in 15/29 (52%). The 5- and 10-year OS after relapse was 81 ± 8% and 75 ± 10%, respectively (Figure 6).

Among the relapsed patients, four were primarily treated according to EuroNet-PHL-C1, three according to GPOH-HD 2002, 10 according to GPOH-HD 95, eight with MOPP-ABVD and three with radiotherapy alone. For one patient the treatment was not known, and no patient was treated with surgery alone. Eight of the relapsed patients died. They were primarily treated according to GPOH-HD 95 (4, all boys) and with MOPP/ABVD regimens (2 boys, 2 girls). Eight patients were treated with high dose chemotherapy with stem cell rescue in the salvage therapy.

Deceased patients. Eighteen of the 292 children with cHL have died; 10 of them within five years of diagnosis. They were between three and 17 years of age when diagnosed with HL and they passed away from between a few weeks to more than 17 years after diagnosis, with a mean/median survival of 6.4 and 3.6 years, respectively. The sex ratio was M/F = 2.0. Nine of them (50%) had B-symptoms at primary diagnosis and eight were reported with relapse of disease (where 7 died from the disease, 1 died in remission). They suffered from NScHL (n = 15), MCcHL (n = 2) and LDcHL (n = 1) (Table II). None of these patients were in stage I, 12 were in stage II (7% of all stage II patients), three were in stage III (6% of all stage III patients) and three were in stage IV (10% of all stage IV patients). Nine died from HL and/or other lymphoma (7 relapsed, 2 had progressive disease) where the primary diagnosis

Figure 4. EFS, treated before and after 1996, respectively.

Table II. Overview of outcome, all patients.

| | NLPHL | cHL | | | | | Total |
		NS	MC	LD	LR	Unspec	
All patients	42	227	50	4	–	3	334
Relapse	5	25	3	1	–	0	34
Alive	42	212	48	3	–	3	316
CR-1	37	202	47	3	–	3	300
CR-1 (%)	88	89	94	75	–	100	90
Alive> = CR-2	5	10	1	–	–	–	16
Dead	–	15	2	1	–	–	18
Dead in CR-1 (incl two SMN)	–	6	1	0	–	–	7
Dead from HL (seven relapsed, two progressive disease)	–	7	1	1	–	–	9
Dead due to treatment complications	–	1	0	0	–	–	1
Dead in CR-2	–	1	0	0	–	–	1

was HL and biopsy at time of relapse showed HL (n = 6), suspected anaplastic large cell lymphoma (with signs of HL in bone marrow) (n = 1), HL and diffuse large B-cell lymphoma (n = 1), and HL and B-lymphoblastic lymphoma, respectively (n = 1). Among those who died from HL and/or other lymphoma, no patient was in stage I, six were in stage II (2 with B-symptoms), one was in stage IIIB, one was in IVA and one was in IVB at the time of diagnosis. Two developed and died from a second malignancy; breast cancer (n = 1, 16 years after diagnosis of NScHL stage IIB bulky disease, treated with chemotherapy and radiotherapy, no relapse), and myelodysplastic syndrome (MDS) followed by acute myeloblastic leukemia (AML) (n = 1, MDS 4 years after diagnosis of NScHL stage IVB treated with chemotherapy and radiotherapy, no relapse, and AML 2 years after bone marrow transplantation for

MDS). One of the 18 died from stroke soon after the first treatment cycle with chemotherapy. One other had underlying immunodeficiency, chronic Epstein-Barr infection and was treated for HL with CR followed by allogeneic bone marrow transplantation due to the immunodeficiency, and died 1 month after transplantation, reported in CR from HL. One suffered from hemolytic anemia, hemochromatosis and infections and died 15 years after HL diagnosis in CR (sibling died from immunodeficiency). In four cases the cause of death was unknown (death occurred 0.5–17 years after diagnosis with HL). Of those four, one had three relapses and was treated with high dose chemotherapy with stem cell rescue, but died in CR 15 years after diagnosis, approximately 10 years after the high dose therapy

NLPHL

Forty-two cases presented with NLPHL. The median age was 13 years of age (2–16) with the majority of the cases in the age group 10–14 years (n = 23) (Figure 2). The majority was boys, 81% (n = 34 vs. 8). Most of the cases presented in early stages (stage I n = 23 (55%), stage II n = 14 (33%), stage III n = 4 (10%) stage IV n = 1 (2%) and B-symptoms were present in three patients (7%).

Two had radical surgery and no other treatment, three received only radiotherapy, 15 were treated with MOPP/ABVD regimens together with or without radiotherapy (10 vs. 5), 11 according to GPOH-HD 2002 pilot (6 with radiotherapy, 3 without, 2 missing data), five according to GPOH-95 (4 with RT, 1 without), and one according to EuroNet PHL-C1. For five patients the treatment was not known.

Five patients relapsed (12%), with a relapse rate of $16 \pm 7\%$, three of them male, two with B-symptoms, four in stage II, and one in stage I. All patients are still alive with a mean follow-up time of 13 (0.7–25) years.
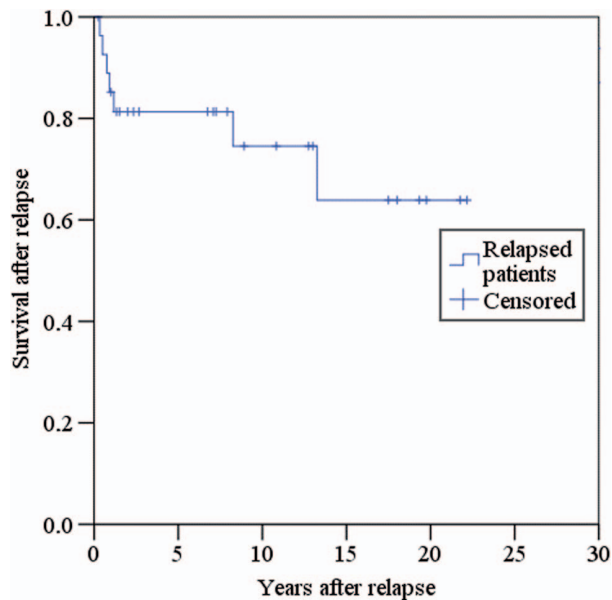

Figure 6. Survival after relapse cHL.

Discussion

Survival rates for children with HL have been very high for a long time, and therefore the reports of early and late effects provide an incentive to find a balance in treatment – to neither over- nor under-treat the young patients with a long life expectancy and to individualize and tailor treatment according to the specific risk profile. However, the high survival rate in HL makes it difficult to identify significant differences and it requires a very large number of patients to be able to draw conclusions that can lead to changes in treatment.

During this period of time, 1985–2009, the radiation fields and doses have been reduced and the primary treatment with chemotherapy has changed to less toxic drugs. The patients in our material have received less radiotherapy in the first-line treatment during the period studied, especially in the latest protocol, EuroNet PHL-C1, where FDG-PET has been used to stratify treatment. No significant difference in OS or EFS was observed when comparing the two time period groups (Figures 4 and 5, respectively) and the Swedish results are comparable to the best in the world [16]. Patients with relapsed disease have lower OS. Compared to other cancer groups in children, the salvage gap, i.e. the chance of surviving despite relapse, is still relatively high. Stage IIB has a significantly lower EFS compared to the other stages in the same treatment group, indicating that B-symptoms may be of greater importance than number of engaged sites (IIB vs. IIAE/IIIA). The same pattern has also been shown in adults with HL in Sweden [17, 18]; especially in patients with bulky disease. Unfortunately, there is no reliable data on bulky disease in the Swedish Childhood Cancer Register. Stage IIB with extra nodular engagement is treated more intensively, following TG3 recommendations. It could be discussed whether all stage IIB patients should be upgraded to more intense treatment.

We have also observed a higher frequency of advanced stages in the later time period, which might be due to better imaging techniques. This possible drift in stages could imply that patients during the later period have received more intensive treatment, which may have affected the survival rates.

Boys are overrepresented in the whole material, with a sex ratio of 1:65, and this is even more pronounced in younger age groups, which is congruent with earlier studies [19, 20]. Among the relapsed patients the ratio is 2:1. This is not a statistically significant difference but indicates a trend. Eleven of the relapsed patients were treated according to GPOH-95 and eight of them were boys. This protocol has reported slightly poorer disease-free survival for boys [11]. Also among those treated with MOPP/ABVD regimens relapse in boys predominates (7 vs. 3). Among those treated according to EuroNet-PHL-C1 the sex relapse rate ratio is 1:1 (2 vs. 2). The finding that male sex may be an unfavorable risk factor in children is in line with the situation in adults where male sex is considered an unfavorable risk factor when stratifying treatment [21].

NScHL is the most dominant subgroup among 15–17 year olds (79%), but it only contributed to 18% of the cases in 0–4 year olds. In MCcHL a contrary pattern was seen where 73% of the cases occurred among the youngest and only 10% in the 15–17-year-old age group. This is consistent with earlier findings in the industrialized world [22].

Among the deceased patients where patient charts have been studied in this material we have found secondary malignancies in two patients and NHL at relapse in three patients. The extent to which the patients who are still alive have suffered or suffer from any secondary malignancy is not known. We have no reliable data from this register on how frequent other secondary side effects of the treatment are. This would require further research including cross-checking with the Swedish National Cancer Register, and targeted clinical follow-up for cardiac, pulmonary, endocrinological and muscular dysfunctions.

As this is a retrospective study the difficulty to differ between results from changes in therapy and results from better supportive care should be taken into account when interpreting the outcomes.

All register-based studies have limitations and the quality of the registers is dependent on how the information is reported and documented. Sweden is known to have high quality registers. The Swedish Childhood Cancer Register has been compared with the Swedish National Cancer Register and was found to be of comparable quality.

Earlier studies have reported considerable misclassification of non-HLs as well as HL [23, 24]. In this study, a sample (71 patients diagnosed in Uppsala and Stockholm, 21% of the tumors) were re-evaluated by an experienced lymphoma specialized pathologist. Only one patient was reclassified as non-HL. Extrapolating these numbers for the whole material would give a misclassification rate of 1.4%, which is lower than in most other studies. However, this rate can only be seen as an indication, since quality of pathology might differ between centers and over time.

During the period studied we have not been able to detect any indications of changes in survival. This could indicate that changes in treatment have not influenced the EFS or OS. Other possible explanations could be better supportive care, a drift to more advanced stages in the later period (leading to more intensive treatment) or a lack of power to detect a

small difference. Survival rates in Sweden are high, comparable to the best in the world, and even after relapse the chances of cure are high. All patients in stage I are still alive. Patients with B-symptoms tended to have lower EFS. Stage IIB had lower EFS compared to the other stages in the same risk group (TG2). We were not able to identify any other characteristics at time of diagnosis specific for the group of patients who did not survive.

References

[1] Swedish Childhood Cancer Registry. Gustafsson G, Kogner P, Heyman M. Childhood cancer incidence and survival in Sweden 1984–2010. Report 2013. Stockholm: Karolinska Institutet; 2013.

[2] http://www.socialstyrelsen.se/statistik/statistikdatabas/cancer [Internet]. 2013 Dec.

[3] van Leeuwen FE, Klokman WJ, Veer MB, Hagenbeek A, Krol AD, Vetter UA, et al. Long-term risk of second malignancy in survivors of Hodgkin's disease treated during adolescence or young adulthood. J Clin Oncol 2000; 18:487–97.

[4] Swerdlow AJ, Barber JA, Hudson GV, Cunningham D, Gupta RK, Hancock BW, et al. Risk of second malignancy after Hodgkin's disease in a collaborative British cohort: The relation to age at treatment. J Clin Oncol 2000;18: 498–509.

[5] Schellong G, Riepenhausen M, Bruch C, Kotthoff S, Vogt J, Bolling T, et al. Late valvular and other cardiac diseases after different doses of mediastinal radiotherapy for Hodgkin disease in children and adolescents: Report from the longitudinal GPOH follow-up project of the German-Austrian DAL-HD studies. Pediatr Blood Cancer 2010; 55:1145–52.

[6] Galper SL, Yu JB, Mauch PM, Strasser JF, Silver B, Lacasce A, et al. Clinically significant cardiac disease in patients with Hodgkin lymphoma treated with mediastinal irradiation. Blood 2011;117:412–8.

[7] van Leeuwen-Segarceanu EM, Dorresteijn LD, Pillen S, Biesma DH, Vogels OJ, van Alfen N. Progressive muscle atrophy and weakness after treatment by mantle field radiotherapy in Hodgkin lymphoma survivors. Int J Radiat Oncol Biol Phys 2012;82:612–8.

[8] Behringer K, Mueller H, Goergen H, Thielen I, Eibl AD, Stumpf V, et al. Gonadal function and fertility in survivors after Hodgkin lymphoma treatment within the German Hodgkin Study Group HD13 to HD15 trials. J Clin Oncol 2013;31:231–9.

[9] van Beek RD, van den Heuvel-Eibrink MM, Hakvoort-Cammel FG, van den Bos C, van der Pal HJ, Krenning EP, et al. Bone mineral density, growth, and thyroid function in long-term survivors of pediatric Hodgkin's lymphoma treated with chemotherapy only. J Clin Endocrinol Metab 2009; 94:1904–9.

[10] Mauz-Korholz C, Hasenclever D, Dorffel W, Ruschke K, Pelz T, Voigt A, et al. Procarbazine-free OEPA-COPDAC chemotherapy in boys and standard OPPA-COPP in girls have comparable effectiveness in pediatric Hodgkin's lymphoma: The GPOH-HD-2002 study. J Clin Oncol 2010; 28:3680–6.

[11] Dorffel W, Ruhl U, Luders H, Claviez A, Albrecht M, Bokkerink J, et al. Treatment of children and adolescents with Hodgkin lymphoma without radiotherapy for patients in complete remission after chemotherapy: Final results of the multinational trial GPOH-HD95. J Clin Oncol 2013;31: 1562–8.

[12] Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, et al. WHO classification of tumours of haematopoietic and lymphoid tissues. Lyon, France: IARC Press; 2008.

[13] Diehl V, Sextro M, Franklin J, Hansmann ML, Harris N, Jaffe E, et al. Clinical presentation, course, and prognostic factors in lymphocyte-predominant Hodgkin's disease and lymphocyte-rich classical Hodgkin's disease: Report from the European Task Force on Lymphoma Project on Lymphocyte-Predominant Hodgkin's Disease. J Clin Oncol 1999;17: 776–83.

[14] Schwartz CL. Special issues in pediatric Hodgkin's disease. Eur J Haematol Suppl 2005:55–62.

[15] Lister TA, Crowther D, Sutcliffe SB, Glatstein E, Canellos GP, Young RC, et al. Report of a committee convened to discuss the evaluation and staging of patients with Hodgkin's disease: Cotswolds meeting. J Clin Oncol 1989; 7:1630–6.

[16] Kelly KM, Hodgson D, Appel B, Chen L, Cole PD, Horton T, et al. Children's Oncology Group's 2013 blueprint for research: Hodgkin lymphoma. Pediatr Blood Cancer 2013;60:972–8.

[17] Glimelius I, Molin D, Amini RM, Gustavsson A, Glimelius B, Enblad G. Bulky disease is the most important prognostic factor in Hodgkin lymphoma stage IIB. Eur J Haematol 2003;71:327–33.

[18] Amini RM, Enblad G, Gustavsson A, Ekman T, Erlanson M, Haapaniemi E, et al. Treatment outcome in patients younger than 60 years with advanced stages (IIB-IV) of Hodgkin's disease: The Swedish National Health Care Programme experience. Eur J Haematol 2000;65:379–89.

[19] Punnett A, Tsang RW, Hodgson DC. Hodgkin lymphoma across the age spectrum: Epidemiology, therapy, and late effects. Semin Radiat Oncol 2010;20:30–44.

[20] Sjoberg J, Halthur C, Kristinsson SY, Landgren O, Nygell UA, Dickman PW, et al. Progress in Hodgkin lymphoma: A population-based study on patients diagnosed in Sweden from 1973–2009. Blood 2012;119:990–6.

[21] Hasenclever D, Diehl V. A prognostic score for advanced Hodgkin's disease. International Prognostic Factors Project on Advanced Hodgkin's Disease. N Engl J Med 1998;339: 1506–14.

[22] Bazzeh F, Rihani R, Howard S, Sultan I. Comparing adult and pediatric Hodgkin lymphoma in the Surveillance, Epidemiology and End Results Program, 1988–2005: An analysis of 21 734 cases. Leuk Lymph 2010;51:2198–207.

[23] Jarrett RF, Krajewski AS, Angus B, Freeland J, Taylor PR, Taylor GM, et al. The Scotland and Newcastle epidemiological study of Hodgkin's disease: Impact of histopathological review and EBV status on incidence estimates. J Clin Pathol 2003;56:811–6.

[24] Glaser SL, Dorfman RF, Clarke CA. Expert review of the diagnosis and histologic classification of Hodgkin disease in a population-based cancer registry: Interobserver reliability and impact on incidence and survival rates. Cancer 2001;92:218–24.