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Venous thrombosis in children and adolescents with Hodgkin lymphoma in Sweden

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ABSTRACT

Introduction: Pediatric patients with Hodgkin lymphoma (HL) have several risk factors for venous thromboembolism (VTE). Although these patients are occasionally treated with thromboprophylaxis, no guidelines are implemented in Sweden. Scarce data from adult patients indicate an increased risk of VTE, but pediatric data is largely missing. Given the favorable overall survival of HL, there should reasonably be more focus on preventing complications.

Materials and methods: We conducted a retrospective cohort study, including all patients registered in the Childhood Cancer Registry under the age of 18 years diagnosed with HL between January 2005 and December 2015 in Sweden.

Results: Data was retrieved from the medical records of all 163 patients (100%) at six Swedish pediatric cancer centers. The incidence of VTE was 7.7% (symptomatic VTE 3.9%). The median follow-up was 3.4 years (range 0.3–10.5). Only five patients (3.1%) were treated with thromboprophylaxis. All VTE events occurred in the older age category (11–17 years) and all but one (92.7%) had a mediastinal mass. While the VTE did not significantly affect the treatment of HL, it caused increased morbidity and 2/12 developed a post-thrombotic syndrome. No significant risk factors for VTE were identified.

Conclusions: VTE is a relatively common complication of HL and its treatment, causing increased acute and long-term morbidity. However, due to limited number of events we could not demonstrate risk-factors for VTE that would identify patients who might benefit from thromboprophylaxis.

1. Introduction

Hodgkin Lymphoma (HL), a malignant neoplasm of the lymphatic system characterized histologically by the Reed-Sternberg-cells, was associated with poor prognosis only a few decades ago. After the introduction of radiotherapy and subsequently combination chemotherapy and radiotherapy, survival increased drastically. With improved long-term survival rates, the treatment strategies have focused on risk-stratification and adapting the therapy to avoid over- or under-treatment, aiming at decreasing toxicities and late complications without jeopardizing event-free survival (EFS) [1].

One major complication of cancer and cancer treatment is venous thromboembolism (VTE). Known pro-thrombotic risk factors in children with cancer include older age (adolescence), systemic inflammation, central venous catheters (CVCs), asparaginase- and steroid therapy, thrombophilia, infections/sepsis, obesity, immobilization and advanced disease [2–5]. The majority of studies in the field of thromboembolism and pediatric cancer describe children with acute lymphoblastic leukemia (ALL) [2,6]. Patients with HL have several risk factors for VTE: all patients have CVCs and are exposed to high-dose corticosteroids, they often already entered puberty, several present with a

Abbreviations: ALL, acute lymphoblastic leukemia; BMI, body mass index; EFS, event-free survival; EuroNet-PHL, European Network for Paediatric Hodgkin's Lymphoma; CI, confidence Interval; COPP, cyclophosphamide, vincristine, procarbazine, prednisolone; COPDAC, cyclophosphamide, vincristine, dacarbazine, prednisolone; CSVT, cerebral sinus venous thrombosis; CVC, central venous catheter; FDG-PET, fluorodeoxyglucose -positron emission tomography; GPOH-HD, German Society of Pediatric Oncology and Hematology - Hodgkin Disease; HL, Hodgkin lymphoma; IOTF, International Obesity Task Force; LMWH, low molecular weight heparin; NOACs, novel oral anticoagulants; OEPA, vincristine, etoposide, prednisolone, doxorubicin; OPPA, vincristine, procarbazine, prednisolone, doxorubicin; PE, pulmonary embolism; TG, therapy group; VKA, vitamin K antagonists; VTE, venous thromboembolism.

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mediastinal mass, a systemic inflammatory response at diagnosis and infections during chemotherapy. United Kingdom and US guidelines recommend thromboprophylaxis for adult cancer patients with risk factors for thrombosis, provided that the risk of bleeding is low [7–9]. HL patients are managed mostly in outpatient setting. For ambulatory adult outpatients with malignancy and no additional risk factors for VTE routine thromboprophylaxis with low molecular weight heparin (LMWH) is not suggested and prophylactic use of vitamin K antagonists (VKA) is not recommended [8]. So far, no guidelines for children have been implemented. The pediatric patients with HL are often teenagers who have gone through puberty; therefore one could assume that guidelines intended for adults would be relevant in this patient group as well. Prophylactic anticoagulation treatment is occasionally initiated when the risk for VTE is estimated to be high, but not systematically and without clear criteria.

During the last decade the clinical treatment protocols used to treat children with HL in Sweden have been updated several times [1]. The changes in treatment strategies over time have focused on decreasing the risk of late complications and toxicity without compromising EFS. Despite the gradual changes in treatment strategy over time, the design of the chemotherapy regimens has remained similar and all protocols include high-dose corticosteroids [10]. The aim of this retrospective study was to estimate the incidence and evaluate the clinical significance of VTE in children and young adults with Hodgkin lymphoma and to characterize the use of prophylactic anticoagulation in this patient cohort in Sweden.

2. Materials and methods

2.1. Study design and data collection

We included all patients below 18 years of age diagnosed with Hodgkin lymphoma identified in the Swedish Childhood Cancer Registry from January 2005 through December 2015. During this period of time, all patients were treated according to active treatment protocols or treatment guidelines from the GPOH-HD (German Society of Pediatric Oncology and Hematology - Hodgkin Disease) or EuroNet-PHL (European Network for Paediatric Hodgkin's Lymphoma) with an OEPA/OPPA-COPP/COPDAC chemotherapy backbone. Initially the chemotherapy for localized disease (therapy group (TG) 1) consisted of two courses of either OEPA (vincristine, etoposide, prednisolone and doxorubicin) for boys, or OPPA (vincristine, procarbazine, prednisolone and doxorubicin) for girls. Patients with more advanced disease (TG 2–3) received further chemotherapy with 2–4 courses of COPP (cyclophosphamide, vincristine, procarbazine and prednisolone). Involved fields radiotherapy was given to all patients in TG 2–3. During the study period, procarbazine in OPPA and COPP was replaced by etoposide (OEPA) and dacarbazine (COPDAC) respectively to reduce gonadotoxicity. From 2007 the therapy was response-adapted based on the results of fluorodeoxyglucose (FDG)-positron emission tomography (PET) after 2 cycles of chemotherapy. Only patients with inadequate response at restaging received radiotherapy [1,11]. Data were collected from the medical records at the six university hospitals in Sweden treating children with cancer, using a questionnaire including detailed background information of the disease, such as date of diagnosis, sub-type of HL, stage at diagnosis, treatment protocol, therapy group, relapses, and, when applicable, prophylactic treatment with anticoagulants. In the event of VTE – information regarding symptoms, clinical, radiological and laboratory findings (including parameters for coagulation, inflammation and blood cultures at diagnosis of VTE), choice of and possible complications of anticoagulation were registered. The outcome of the VTE as well as possible consequence of VTE on HL prognosis and treatment (such as treatment delays or replacement of CVCs) was also collected. The study was approved by the Regional Ethical Review Board in Stockholm (reference number 2015/2046-31/2).

2.2. Statistical analysis

Statistical analyses were performed using SPSS, Version 20 for Windows (SPSS Inc. Chicago, IL). Comparison of continuous variables was performed using the Mann Whitney *U* test and categorical variables with the Chi-squared test. Body mass index (BMI) was adjusted to age and gender according to International Obesity Task Force (IOTF) BMI cut-offs. The incidence of thrombosis was estimated using logistic regression, and 95% confidence interval (CI) excluding non-VTE patients with a follow-up period of less than six months. Two-sided *P*-values < 0.05 were considered significant.

3. Results

3.1. Study population and baseline characteristics

In total, 163 children and adolescents were diagnosed with HL in Sweden during the study period of 11 years. Complete data was obtained from all patients (100%). The clinical characteristics of the study cohort are presented in Table 1. One hundred sixty patients had a CVC (134 had fully implanted subcutaneous injection ports and 26 had external lines). In addition, seven of the patients with subcutaneous injection ports first had a temporary external line; four patients had their subcutaneous injection port replaced to external line and one to a new subcutaneous injection port. One of the patients with an external line had a new external catheter inserted. Two patients underwent surgery only and did not receive chemotherapy or radiotherapy, and three patients received other chemotherapy than described above. The median follow-up time for the study cohort was 3.4 years (mean 3.9, range 0.3–10.5). All patients were alive at the end of the follow up, 16 (9.8%)

Table 1
Demographic characteristics of children and adolescents with Hodgkin lymphoma.

Variable	HL, all $n = 163$	No VTE 151 (92.6%)	VTE 12 (7.4%)	*P*-value
Sex				0.549
Female	74 (45.4)	70 (46.4)	4 (33.3)	
Male	89 (54.6)	81 (53.3)	8 (66.7)	
Type				0.778
Nodular sclerosis	121 (74.2)	111 (73.5)	10 (83.3)	
Mixed cellularity	15 (9.2)	14 (9.3)	1 (8.3)	
Lymphocyte-depletion	0 (0)	0 (0)	0 (0)	
Lymphocyte rich	0 (0)	0 (0)	0 (0)	
Nodular lymphocyte predominant	17 (10.4)	17 (11.3)	0 (0)	
HL NOS	10 (6.1)	9 (6.0)	1 (8.3)	
Stage				0.596
I	10 (6.1)	10 (6.6)	0 (0)	
II	90 (55.2)	82 (54.3)	8 (66.7)	
III	33 (20.2)	30 (19.9)	3 (25.0)	
IV	30 (18.3)	29 (19.2)	1 (8.3)	
Therapy group				0.979
1	50 (30.7)	46 (30.5)	4 (33.3)	
2	47 (28.8)	43 (28.5)	4 (33.3)	
3	54 (33.1)	5 (3.3)	4 (33.3)	
Unknown	12 (7.4)	12 (7.9)	0 (0)	
Mediastinal involvement				0.467
Yes	127 (77.9)	116 (76.8)	11 (91.7)	
No	36 (22.1)	35 (23.2)	1 (8.2)	
BMI – age and gender adjusted[a]				0.642
Underweight	15 (10.0)	13 (8.6)	2 (16.7)	
Normal	104 (69.3)	97 (64.2)	7 (58.3)	
Overweight	31 (20.7)	29 (19.2)	2 (16.7)	
Change of CVC[b]				0.057
Yes	13 (8.0)	10 (6.6)	3 (25.0)	
No	150(92.0)	141(93.4)	9 (75.0)	

HL = Hodgkin lymphoma; VTE = Venous thromboembolism; lymphoma HL NOS = Hodgkin lymphoma not otherwise specified; BMI = body mass index; CVC = central venous catheter.

[a] Data on BMI was missing from 13 patients.

[b] Insertion of a new CVC due to relapse not included.