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Hodgkin lymphoma in Tyrol—a population-based study

Dominic Fong · Michael Steurer · Richard Greil ·
Eberhard Gonsilius · Gilbert Spizzo · Guenther Gastl ·
Alexandar Tzankov

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Abstract We aimed to analyze the epidemiology, clinical characteristics, and outcome of patients with Hodgkin lymphoma (HL) diagnosed in Tyrol. All patients with newly diagnosed HL between 1993 and 2005 were included in this study. Among the 158 cases included, nodular lymphocytic predominant HL (nodular paragranuloma) was identified in ten cases (6%) whereas the majority of patients had classical Hodgkin lymphoma. Age ($p < 0.01$), sex ($p = 0.03$), risk groups according to the German Hodgkin Study Group stratification ($p < 0.01$), and bone marrow infiltration ($p < 0.01$) were of prognostic significance considering overall survival (OS) whereas histological subtype and bulky disease were not. The 5- and 10-year OS rates for the total group were 89% and 85%, respectively. Notably, in patients with advanced-stage HL ($n = 49$), combined modality treatment resulted in significantly better OS than chemotherapy alone ($p = 0.01$). Three patients developed a second hematological malignancy and one patient developed breast cancer. However, five patients

(3%) had a malignant hematological disorder before occurrence of HL. Concerning treatment-related toxicity, bleomycin-associated lung toxicity was observed in six (4%) patients and five (3%) developed lethal treatment-related infectious complications. Our results provide evidence that the incidence rate of HL in Tyrol is comparable to other Western countries. Modern risk-adapted treatment results in excellent long-term prognosis but may be complicated by serious nonhematological side effects, in particular, infections and bleomycin-induced lung toxicity. Furthermore, 3% of HL patients had an antecedent malignant hematological disease before occurrence of HL.

Keywords Hodgkin lymphoma · Population-based study · Tyrol · Hodgkin's disease

Introduction

Hodgkin lymphoma (HL) has an annual incidence of two to three cases per 100,000 person-years and comprises about 25% of malignant nodal lymphomas worldwide [1]. In developed countries, the incidence rate has slightly decreased in the last 20 years and, based on modern systemic oncologic treatments, survival has improved markedly over time [2]. HL is characterized morphologically by the presence of distinctive neoplastic giant cells, Hodgkin and Reed-Sternberg (HRS) cells, which are embedded in a reactive cellular background [3]. For a long time, the neoplastic nature of the HRS cells was highly controversial but nowadays it is clear that HL is a lymphoproliferative disease mostly of B cell nature [4]. According to the World Health Organization (WHO) classification, two biologically and clinically different entities are distinguished: nodular lymphocytic predominant HL (NLPHL, nodular paragranuloma) and classical

D. Fong (✉) · M. Steurer · E. Gonsilius · G. Gastl
Department of Hematology and Oncology,
Innsbruck Medical University,
Anichstrasse 35,
6020 Innsbruck, Austria
e-mail: dominic.fong@i-med.ac.at

R. Greil
Third Medical Department of the Salzburg
General Hospital and Private Paracelsus University,
Salzburg, Austria

A. Tzankov
Department of Pathology, Universitaetsspital Basel,
Basel, Switzerland

G. Spizzo
Department of Hematology and Oncology,
Franz Tappeiner Hospital,
Merano, Italy

Hodgkin lymphoma (cHL), the latter entity including nodular sclerosis (NS), mixed cellularity (MC), lymphocyte-rich and lymphocyte depletion (LD) cHL [5]. cHL comprises approximately 95% of all HL cases and shows a bimodal age distribution with a major peak in young adults and a minor peak in late life. In contrast, NLPHL can occur at any age but there is a peak of incidence in the fourth decade [6]. NS is the predominant histological subtype in developed countries, whereas MC is more frequent in developing countries. Several risk factors have been described to be associated with the development of HL [7–10]. The presence of Epstein-Barr virus (EBV) in HRS cells may be related to prognosis in some instances [11–13]. EBV is a ubiquitous herpes virus of known oncogenic potential, which can be detected in the malignant HRS cells of 30% to 100% of HL patients, dependent on the geographic area [14, 15].

The prognosis and management of HL is dictated by disease stage and other risk factors rather than histology [16]. Depending on stage and risk factor profile, on average, more than 80% of patients with HL can be cured with effective first-line therapy [17]. Today, doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD), often combined with involved field radiotherapy, is the most commonly applied treatment regimen and is standard treatment for patients with early-stage disease without additional risk factors [18–22]. For advanced-stage HL, the (dose-escalated) bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP) protocol has been shown to be superior to less-intensive regimens [23]. The major drawback that hampers the clinical achievements during the last decades is the increasing incidence of late toxicities and treatment complications. Of note, secondary malignancies seem to be a major cause of morbidity and mortality among long survivors of HL [24, 25].

In this population-based study, taking the advantage of the demographically well-documented population of Tyrol (<http://www.tirol.gv.at/themen/zahlenundfakten/statistik>), we retrospectively investigated the epidemiological and clinical characteristics of all HL patients diagnosed within the period from 1993 to 2005 and analyzed treatment outcomes, toxicities, and long-term results as well as antecedent and subsequent malignancies.

Materials and methods

Patients

The demographic and clinical data of all patients are listed in Table 1. Our study comprised 158 patients without evidence of HIV infection diagnosed with HL between 1 January, 1993 and 30 June, 2005 at the Institute of Pathology at the Medical University of Innsbruck. Inci-

Table 1 Demographic and clinical data of patients

Characteristics	Patient cHL		Patient NLPHL	
	No	%	No	%
Age group				
0–35	64	(44)	4	(40)
36–55	42	(28)	6	(60)
over 55	42	(28)		
All	148		10	
Sex				
Male	78	(53)	5	(50)
Female	70	(47)	5	(50)
Histology				
NS	95	(64)		
MC	44	(30)		
LP	4	(3)		
Unclassifiable	5	(3)		
Latent membrane protein1				
Yes	24	(16)		
No	53	(36)		
Unknown	71	(48)		
Stage (according to GHSG)				
Favorable	39	(26)	3	(30)
Intermediate	39	(26)	2	(20)
Advanced	55	(38)	5	(50)
Unknown	15	(10)		
Presence of risk factors				
No	43	(29)	4	(40)
Yes	87	(59)	6	(60)
Unknown	18	(12)		
B symptoms				
No	78	(53)	8	(80)
Yes	57	(38)	2	(20)
Unknown	13	(9)		
Bone marrow involvement				
No	135	(92)	10	(100)
Yes	8	(5)		
Unknown	5	(3)		
Therapy modality				
ABVD	70	(47)	5	(50)
based + RTX				
BEACOPP	15	(10)	1	(10)
based + RTX				
ABVD based	23	(16)	3	(30)
BEACOPP based	13	(9)		(10)
RTX alone	4	(3)		
Other	3	(2)		
Unknown	20	(13)	1	
Treatment				
Outside trial	99	(67)	8	(80)
In trial	49	(33)	2	(20)
Relapse				
No	128	(87)	7	(70)
Early	8	(5)	3	(30)
Late	10	(7)		
Unknown	2	(1)		

dence data were cross-validated with the population-based Cancer Registry of Tyrol, where all lymphopoeitic malignancies are recorded together with corresponding patient data. The median observation period was 46 months (range, 3 to 148). All patients were newly diagnosed by histopathology. Data collection and analysis were performed according to current data safety law and institutional review board regulations. No patient was excluded, irrespective of age and performance status. Clinical data were obtained by reviewing the charts and contacting the physicians in charge in different hospitals. The staging procedures included clinical history, physical examination, routine laboratory, chest X-ray, abdominal sonography, computed tomography scans of the neck, thorax, abdomen, and pelvis, bone marrow aspiration and biopsy, bone marrow or skeletal radionuclide imaging, and, if necessary, explorative laparotomy. Clinical staging was performed according to the modified version of the Ann Arbor classification that supplements additional information on the absence or presence of the following risk factors [26]: (1) three or more involved areas, (2) large mediastinal mass ($\geq 1/3$ of thoracic diameter), (3) extranodal disease extension, and (4) elevated erythrocyte sedimentation rate (≥ 50 mm/h without or ≥ 30 mm/h with B symptoms). Bulky disease was defined as a nodal tumor mass >5 cm. Patients received either standard treatment or therapy according to investigational protocols of the German Hodgkin Study Group (GHSg) that were active at time of the patients' diagnosis. Disease remission was defined as absence of disease for at least 1 month as determined by laboratory and imaging studies as well as physical examination. Disease relapse was defined as disease progression occurring at least 3 months after achieving disease remission. Early relapse required a complete remission lasting ≥ 3 months to 12 months. Late relapse was defined as relapse after complete remission lasting >12 months. Treatment failure was defined as disease relapse or primary treatment resistance. Disease-specific mortality was defined as patient deaths due to or with symptomatic-detectable lymphoma.

Histopathology and immunohistochemistry

All 158 tumors were reclassified on hematoxylin-and-eosin (H&E)- and Giemsa-stained slides and histological type was reassessed according to the current World Health Organization classification [5]. Routinely, all cases were stained for CD15 and CD30 and in 52% of cases for LMP1 if cHL was suspected on H&E-stained slides. In addition, staining for CD20, CD45RA, CD57, and the immunoglobulin J-chain was carried out if NLPHL was suspected.

Standard immunoperoxidase techniques were applied using an automated immunostaining device (Nexes[®], Ventana Tucson, AZ, USA) as described previously [27].

Diaminobenzidine was used as chromogen. For negative controls, the primary antibodies were omitted.

Statistics

Current life status data of all patients, including cause of death, were available from the Cancer Registry of Tyrol. Incidence was calculated as sex-specific and age-adjusted standardized incidence rate using Segi's population weighting [28] for the Tyrolean population, which is reported annually by the Tyrolean government (<http://www.tirol.gov.at/themen/zahlenundfakten/statistik>). Statistical analysis was performed using the Statistical Software Package of Social Sciences 15.0, applying descriptive methods, Pearson χ^2 and Mann–Whitney U test. Time trend curves were constructed using the curve estimation option. For investigation of the annual incidence changes, a least-square regression analysis of the standardized incidence rate weighted by the absolute number of cases was applied. Survival was estimated by the Kaplan–Maier method and compared by the log-rank test. p values <0.05 were considered significant.

Results

The main characteristics of the study population are summarized in Table 1. The median age at diagnosis of cHL was 39 years (range, 10–85 years) and 36 years (range; 14–51) for NLPHL. Similar to that reported from other cancer registries, the age-adjusted incidence rate was 1.98 (1.2–2.9) per 100,000 person-years. Depending on the absence or presence of risk factors according to the GHSg, 42 (27%) patients were diagnosed with favorable disease, 41 (26%) with intermediate, and 60 (38%) with advanced disease, respectively. In 15 cases, the risk factors according to the GHSg were unknown. Fifty one (32%) of the patients were enrolled in clinical trials of the GHSg. Risk-adapted treatment given according to GHSg stratification criteria is summarized in Table 2. The 5- and 10-year overall survival (OS) rates for the patients with cHL were 89% and 85%, respectively, whereas all ten patients with NLPHL are still alive (Fig. 1). NS was, as expected, the predominant histological subtype (64%) and occurred more frequently in younger individuals, while MC cHL was more commonly seen in the elderly.

In cHL, patients' age ($p<0.01$), sex ($p=0.03$), risk groups according to the GHSg stratification ($p<0.01$; Fig. 2), presence of B symptoms ($p<0.01$), and bone marrow infiltration ($p<0.01$) were of prognostic significance regarding OS, whereas histological subtype, extranodal involvement (except bone marrow), and bulky disease were not. Data on the EBV status were available only for a subgroup of 77 patients (52%) and therefore not sufficient for valid subgroup analyses. Patients enrolled in clinical trials of the

Table 2 Treatment of HL variants according to GHSG stages

	cHL (n)	NLPHL (n)
Treatment of favorable stages		
IF-RT	2	
ABVD + RT	24	3
ABVD	8	
Treatment of intermediate stages		
ABVD + RT	28	1
ABVD	4	
BEACOPP + RT	6	1
BEACOPP	1	
Treatment of advanced stages		
ABVD + RT	14	1
ABVD	10	3
BEACOPP + RT	9	
BEACOPP	12	
Other	3	
Unknown	27	1

GHSG showed a trend towards better OS than patients being treated outside trials (Fig. 3). Notably, patients with advanced-stage HL ($n=49$), who received combined modality treatment according to the GHSG, had significantly better OS than those treated by chemotherapy alone ($p=0.01$; Fig. 4). The relapse rate in 156 patients for whom complete follow-up data were available was 13%; 11 (7%) patients (eight cHL, three NLPHL) had early and ten (6%) patients (all cHL) late relapses, respectively. Within the median observation period of 45 months (range 3–148), three of 146 patients (2%) with cHL developed a second hematological malignancy: two secondary acute myelogenous leukemias and one diffuse large B cell lymphoma. Furthermore, one female patient (0.6%) developed breast cancer. The details of

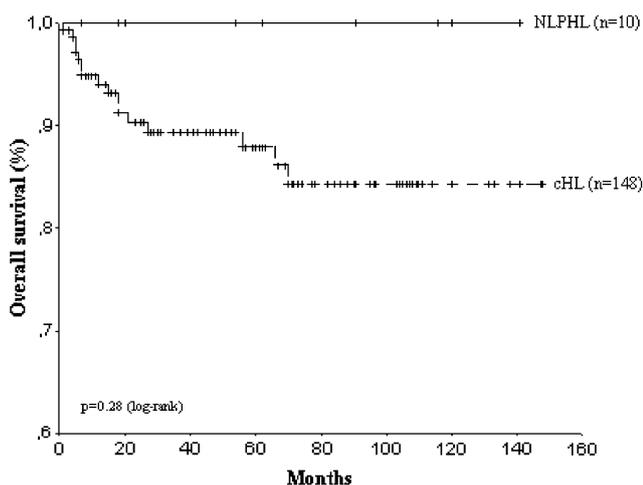


Fig. 1 Overall survival of patients with cHL and NLPHL diagnosed between 1993 and 2005 in Tyrol. The 5- and 10-year overall survival rates for the patients with cHL were 89% and 85%, respectively. All ten patients with NLPHL are still alive

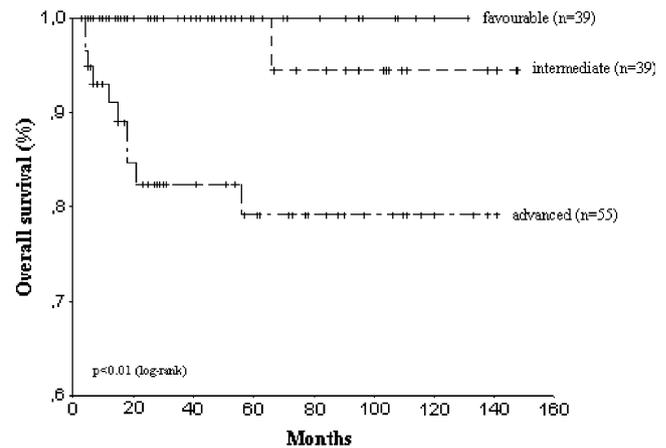


Fig. 2 Overall survival of cHL patients, to whom the GHSG risk-group stratification could be applied. Patients with favorable and intermediate stage had a significantly better overall survival rate than patients in advanced-stage disease as assessed by log-rank test ($p<0.01$)

all second malignancies are listed in Table 3. All four cHL patients developing a secondary neoplasia had received a combined modality treatment with cyclophosphamide, vincristine, procarbazine, and prednisone (COPP)–ABVD followed by radiotherapy. Second malignancies occurred on an average of 47 months (range 22–60) after diagnosis of cHL. Moreover, five patients (3%) had already experienced a malignant lymphoproliferative disease preceding cHL which occurred on an average of 97 months (range 37–175) before cHL was diagnosed (Table 3).

Concerning treatment-related toxicity, bleomycin-induced lung toxicity was observed in six (4%) patients (Table 4). Of these, five patients had received ABVD whereas only one patient had been treated according to the BEACOPP protocol. Diagnosis of bleomycin-induced pneumonitis (BIP) was based on clinical symptoms, supported by typical

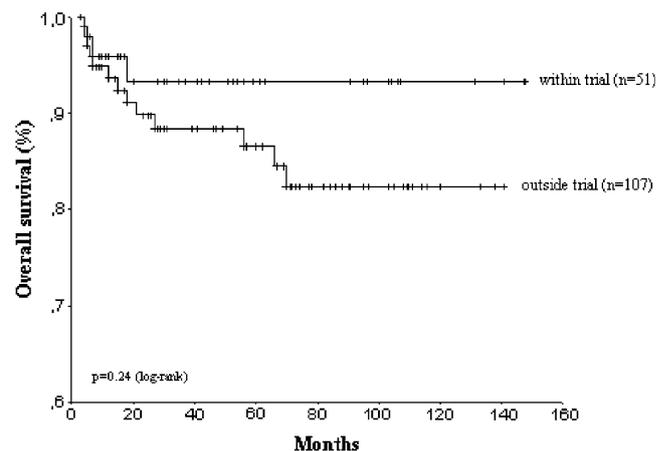


Fig. 3 Fifty one (32%) of patients were enrolled in clinical trials of the GHSG showing a trend towards better overall survival defined by log-rank test ($p=0.2$)

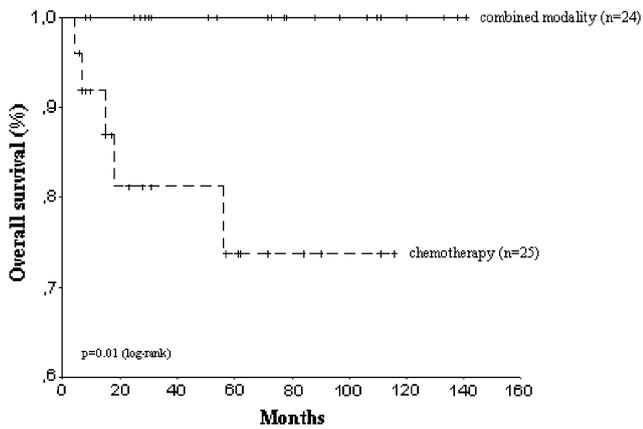


Fig. 4 Overall survival of patients with advanced-stage cHL according to the GHSG stratification. Treatment with combined modality resulted in a significantly better overall survival than with chemotherapy alone (log-rank test, $p=0.01$)

findings on computed tomography examination of the chest and bronchoalveolar lavage. Dose reduction by omitting one or more cycles of chemotherapy was necessary in five patients, whereas treatment of one patient was switched from ABVD to the COPP protocol. All patients recovered

completely following the application of high-dose steroids. Despite dose and protocol modifications, all six patients are still in complete remission.

With respect to infectious complications, five (3%) patients developed lethal treatment-related infections (Table 4): one patient undergoing first-line treatment with BEACOPP died from a disseminated invasive mycosis (*Aspergillus fumigatus*); another two patients died during treatment with BEACOPP due to fatal bacterial infections. Moreover, two patients deceased because of Gram-negative sepsis after receiving salvage chemotherapy. Five (3%) patients died from progressive or recurrent disease and three (2%) due to a secondary malignancy.

Discussion

Our findings in a well-documented patient population of 158 HL that have been diagnosed among Tyrolean inhabitants during the period 1993–2005 are comparable with those reported from large randomized studies conducted by the GHSG. These results provide evidence that patients with HL in Tyrol are treated according to state-of-

Table 3 Second malignancies

Patient		Disease		Therapy	HL				
Sex	Age, years (diagnosis HL)	Diagnosis (month/year)	Type		Diagnosis (month/year)	Subtype	Stage	EBV association	Modality
Second malignancy before HL									
M	71	05/1990	Squamous cell carcinoma	Surgery; RTX	07/1993	MC	IA	n.d.	Combined
M	68	11/1997	CLL	COP; Fludarabine; INF- α ; Gupta et al; Rituximab	05/2004	MC	IIB	LMP +	Radiotherapy
F	81	07/1994	CLL	COP; CHOP; Fludarabine; Alemtuzumab	02/2003	MC	IB	LMP +	Radiotherapy
M	72	03/1983	DLBCL of testis	Semicastration; 4 \times CHOP	11/1997	MC	IIA	LMP +	Combined
F	58	07/1993	DLBCL	6 \times CEOP-/IMVP16-Dexa	12/2001	MC	IIA	n.d.	Combined
F	61	01/1996	FL	6 \times CHOP; IFN- α ; RTX	02/1999	MC	IIA	LMP-	Combined
Second malignancy after HL									
M	50	05/2000	AML	Cytarabine, idarubicin	06/1995	NS	IIA	n.d.	Combined
F	61	02/2004	AML	Sibling-PBSCT; FLAG	02/1999	MC	IIA	LMP-	Combined
F	67	01/1998	DLBCL	6 \times CHOP; 3 \times IMVP16; RTX	04/1996	MC	IIIA	n.d.	Combined
F	27	01/1999	Breast cancer	6 \times Epirubicin/Taxol; mastectomy	03/1995	NS	I B	LMP-	Combined

Table 4 Treatment related toxicity

Patient		Stage HL	Planned treatment	Treatment given
Sex	Age, years (diagnosis HL)			
Bleomycin-induced pneumonitis				
M	72	III A	8× ABVD	6× ABVD
F	77	IIA	4× ABVD	2× ABVD
M	72	IA	4× ABVD + IF-RTX	3× ABVD + IF-RTX
M	68	IIIA	8× ABVD	2× ABVD + 4× COPP
M	59	IIA	4× ABVD + IF-RTX	3.5× ABVD + IF-RTX
F	39	IIIA	8× BEACOPPesc + IF-RTX	4× BEACOPPesc IF-RTX
Lethal infectious complications				
F	36	IIIB	MUD-PBSCT	Bacterial infection
M	61	IIIB	BEACOPPbas	Bacterial infection
F	50	IVB	BEACOPPesc	Bacterial infection
M	51	IIIB	DHAP	Bacterial infection
M	39	IIB	BEACOPPesc	Invasive mycosis

the-art criteria and carry an excellent long-term prognosis with 5- and 10-year OS rates for the total group of 89% and 85%, respectively. The age-adjusted incidence rate for HL has been reported to be 2.7 per 100,000 person-years [29]. In our study, the age-adjusted incidence rate was slightly lower with 1.98 (1.2–2.9) per 100,000 person-years confirming a previous epidemiologic analysis carried out between 1988 and 1992 [30]. Thus, the incidence of HL appears to be rather stable in Tyrol over the last 20 years, which is in keeping with data from other European countries [30, 31].

Nowadays, HL has become one of the most efficiently curable malignancies achieved by appropriate selection of patients for risk-adjusted therapy regimens. However, two major problems remain challenging: development of secondary malignancies as the most serious late complication of HL as well as acute toxicities, particularly myelosuppression, infectious complications, and bleomycin-associated lung toxicity. The malignancies most frequently associated with chemotherapy include acute myeloid lymphoma (AML), myelodysplastic syndromes, and non-Hodgkin lymphomas, whereas solid tumors appear more commonly after radiotherapy [32–36]. The absolute excess risk for secondary neoplasias in patients with HL has been reported to range between 40 and 90 malignancies per 10,000 patient years (0.4% to 0.7% per year) [36, 37]. In line with these data, three (2%) patients of our cohort developed secondary hematological malignancies and one patient (0.6%) developed breast cancer. All four patients had received a combined modality treatment with COPP–ABVD regimen followed by radiotherapy. Second malignancies occurred on an average of 47 months after diagnosis of HL. Moreover, five patients (3%) had a malignant hematological disease before occurrence of

cHL, an issue that has only rarely been addressed before. Of these patients, two developed cHL within a mean of 91 months after diagnosis of B chronic lymphocytic leukemia (CLL). In another two patients, cHL occurred within a mean period of 139 months after diagnosis of diffuse large B cell lymphoma and in one patient cHL was diagnosed 38 months after diagnosis of follicular lymphoma. Both patients with B-CLL who developed an HL variant of Richter's syndrome had received fludarabine. In one of them, we were able to demonstrate a clonal relationship between B-CLL and microdissected HRS cells as reported previously [38]. Whether this co-occurrence of second lymphoproliferative diseases in cHL patients is coincidental or a result of patient's genetical background, making B cells prone to malignant transformation, or due to presence of malignant B stem cells, giving origin to different lymphomas, is currently unclear.

Treatment strategies of HL have changed during the recent years. Since the optimal strategy has not yet been defined, the aim of the current treatment protocols is not only to prolong disease free and OS but also to reduce toxicity. Myelosuppression is a common side effect of BEACOPP regimens and might be complicated by serious bacterial, viral, and fungal infections. Recently, acute hematologic toxicity of the HD9 study patients being treated with BEACOPP regimens has been reported by the GHSG [39]. The occurrence of WHO grade 4 leukopenia was documented in 38% (BEACOPP-baseline) and 92% (BEACOPP-escalated) of the patients. Six patients (1.4%) died from acute toxicity during BEACOPP-baseline therapy and four (0.9%) patients died receiving BEACOPP-escalated, respectively. Specific data on the incidence and cause of infections during both regimens were not fully available due to incomplete documentation. In our retro-

spective study, five (3%) patients died of lethal treatment-related infectious complications. Of these, three patients have been treated first line with BEACOPP regimen and two patients died during high-dose salvage chemotherapy for relapsed cHL. Thus, when applying these regimens, careful monitoring of acute toxicities is of paramount importance inside and outside clinical trials.

Another life-threatening complication is the induction of fatal pulmonary toxicity associated with the use of bleomycin. The preferential pulmonary involvement (along with skin toxicity) in bleomycin toxicity (BIP) can be explained by lack of the bleomycin-inactivating enzyme bleomycin hydrolase in these tissues [40]. With the use of bleomycin, various pulmonary syndromes have been described such as bronchiolitis obliterans with organizing pneumonia [41], eosinophilic hypersensitivity [42], and, most commonly, interstitial pneumonitis. This BIP has been reported in up to 46% of patients treated with bleomycin-containing chemotherapy regimens [43–48]. In the present study, BIP was rather infrequent with six (4%) patients, five receiving ABVD regimen and one BEACOPP, respectively. Recent reports showed a significantly increased risk of BIP in HL patients being treated with bleomycin-containing chemotherapy when granulocyte colony-stimulating factor (G-CSF) was additionally used [49–51]. As G-CSF is widely applied to avoid chemotherapy-associated treatment delays, further attention on this coincidence is warranted.

In conclusion, our retrospective study provides evidence that Tyrol patients with HL are efficiently treated according to the standard of care guidelines or within GHSG trials and have an excellent long-term prognosis. However, even modern treatment regimens leave space for improvement to minimize severe side effects, in particular, infectious complications and BIP.

Disclosure or conflict of interest There is no duality of interest to be disclosed.

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