General condition and comorbidity of long-term survivors of adult acute lymphoblastic leukemia

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Abstract

Cure rates in adult acute lymphoblastic leukemia (ALL) improved using pediatric-based chemotherapy and stem cell transplantation (SCT). However, limited data on the health condition of cured adults are available whereas pediatric data cannot be transferred. The GMALL analyzed the health status in survivors of adult ALL retrospectively. Physicians answered a questionnaire on general condition (Eastern Cooperative Oncology Group [ECOG] status) and comorbidity or syndrome occurrence observed after treatment. Five hundred and thirty-eight patients with a median age of 29 (range, 15-64) years at diagnosis were analyzed, median follow-up was 7 (range, 3-24) years. Thirty-one percent had received SCT. ECOG status was 0-1 in 94%, 34% had not developed significant comorbidities. Most frequent comorbidities involved the neurologic system (27%), endocrine system (20%), skin (18%), graft-*versus*-host-disease (15%), cardiac system (13%), fatigue (13%). SCT impacted ECOG status and comorbidity occurrence significantly. ECOG 0-1 was observed in 86% of SCT and 98% of non-SCT patients ($P<0.0001$); comorbidity was observed in 87% and 57% respectively ($P<0.0001$). Our analysis elucidates the spectrum of comorbidities in cured adult ALL patients, with higher risk for transplanted patients, providing stimulations for the design of adequate aftercare programs. Overall, a large proportion of non-SCT patients achieved unrestricted general condition. The data provide a reference for new patient-centered endpoints in future trials.

Introduction

Outcome of adult acute lymphoblastic leukemia (ALL) has considerably improved using pediatric-based therapies. Complete remission rates reach 90% and survival approaches 60-70% in younger adults.[1,2] Intensive chemotherapy is the mainstay of therapy and patients suffer from acute and long-term toxicities. In addition, more adult compared to pediatric patients display high-risk (HR) features and these patients are often candidates for allogeneic stem cell transplantation (SCT).[3] With improving survival, the incidence and type of comorbidities and late effects is highly relevant. A variety of systematic evaluations of survivors from pediatric neoplasia have been reported.[4-7] Several specific syndromes were described such as disorders of the central

nervous system (CNS), obesity, osteonecrosis, and secondary malignancies (reviewed in [8]). Late effects of SCT include graft-*versus*-host disease (GvHD), cardiovascular, pulmonary, endocrine, or musculoskeletal disorders, and secondary malignancies (reviewed in [9]). Observations in children can, however, not be easily transferred to adult ALL survivors since treatment approaches are different and biological reactions to chemotherapy or irradiation may be different in developing tissues. Overall, limited data are available with respect to the health condition in long-term survivors of adult ALL.

Since 1981, the German Multicenter Study Group for Adult Acute Lymphoblastic Leukemia (GMALL) has completed seven consecutive prospective treatment trials for adults aged between 15 and 65 years. The major focus was risk-adapted subgroup-specific therapy. In order to establish a systematic overview of the health status of long-term survivors i.e., cured ALL patients, the GMALL performed a retrospective study in survivors of six consecutive GMALL trials initiated between 1984 and 2003 (*clinicaltrials gov. Identifier: NCT00198978, NCT00199004, NCT00199017, NCT00199069, NCT00199056* and *NCT00198991*). The aim was to describe the incidence of comorbidities and the potential correlation to patient and disease characteristics.

Methods

Patient characteristics

Patients enrolled in six consecutive GMALL studies for newly diagnosed ALL (age, 15-65 years) were eligible; patients younger than 18 years were only included until 2012. All protocols were based on intensive, pediatric-based chemotherapy according to a BFM backbone, including prophylactic CNS irradiation, intrathecal therapies and consolidation including high-dose (HD) methotrexate and cytarabine followed by maintenance therapy.[10,11,12,13,14] Since trial 06/99 PEG-asparaginase replaced native *E.coli* Asparaginase in first-line therapy. Patients with HR features were candidates for SCT. Figure 1 shows a schematic overview whereas dosing is stated in the *Online Supplementary Table S2*. The studies were conducted in over 100 participating hospitals. All patients agreed to trial participation after informed consent. The trials were reviewed by Ethical Review Boards.

Patients aged between 15 and 65 years were identified in the respective GMALL databases (02/84, 03/87, 04/89, 05/93, 06/99 and 07/03) if they were alive more than 5 years from their diagnosis. Several patients from recent trials 06/99 and 07/03 with shorter follow-up were accepted to gather information on outcomes of these intensified regimens.

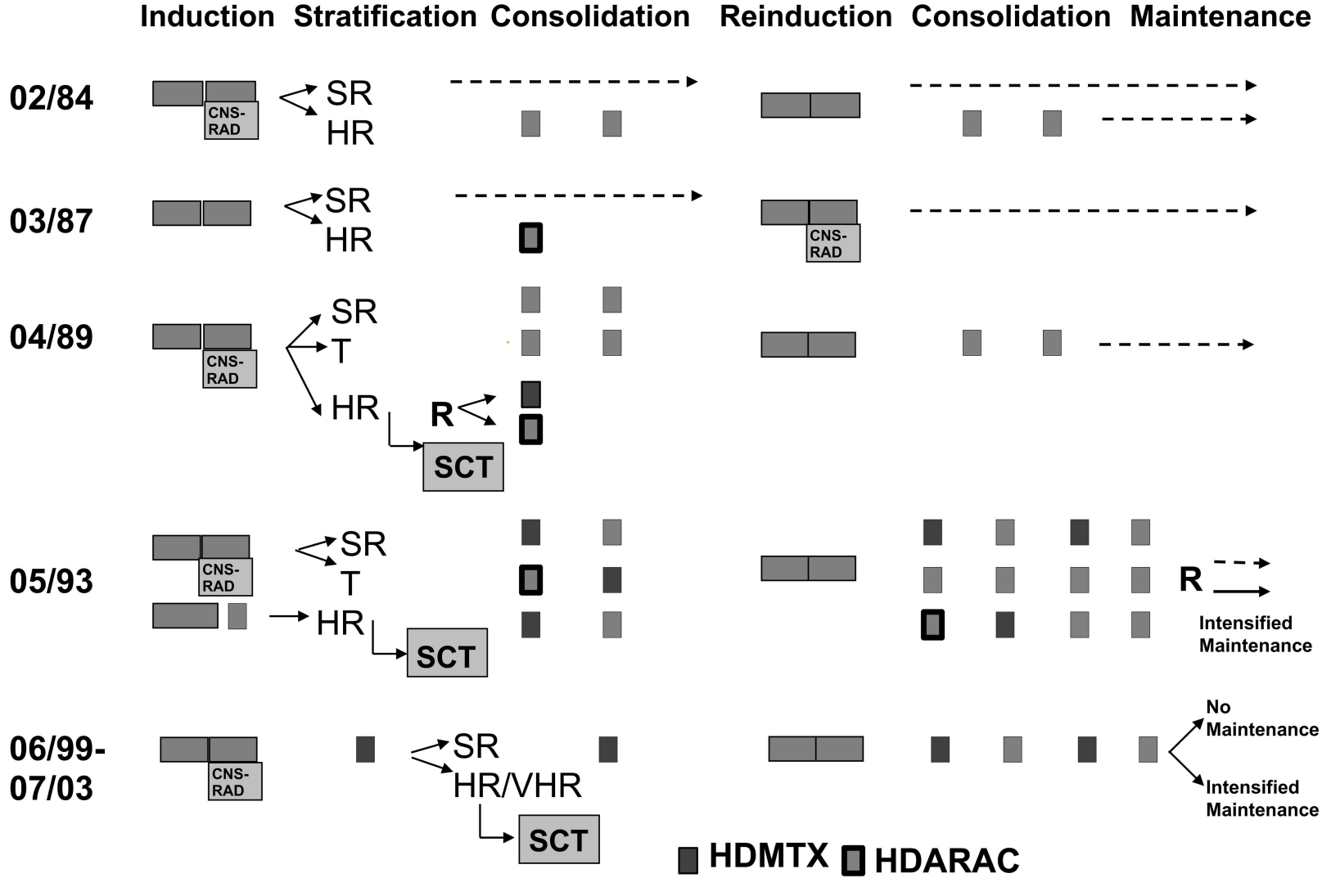

Figure 1. Schematic overview on GMALL trials 02/84 – 07/03. CNS-RAD: central nervous system irradiation 24 Gy; SR: standard risk; HR: high risk; T: T-cell acute lymphoblastic leukemia; VHR: very high risk (Ph/BCR-ABL positive); HDMTX: high-dose methotrexate; HDARAC: high-dose cytarabine; R: randomization; SCT: stem cell tranplantation.

Data collection

The questionnaire was sent to responsible physicians in participating hospitals and included information on surviving patients as identified in the GMALL database. Physicians were asked either to answer the questionnaire or to forward it to the respective practitioners responsible for aftercare. The questionnaires were to be answered in patients alive according to the last follow-up, only. Questions were related to any disease or syndrome documented in patient files after the end of ALL treatment. The questionnaire was divided into three parts. Part 1 addressed any comorbidity observed in one of eight organ systems (skin, lung, neurologic system, endocrine system, kidney/liver, cardiac system, gastrointestinal system, eyes). Part 2 was directed in addition to specific syndromes (e.g., fatigue, GvHD, secondary malignancies, infections, osteonecrosis, hyperthyroidism/ hypothyroidism). Part 3 addressed the general health condition, measured as ECOG performance status at last patient visit. In addition, a classification of severity according to CTCAE was requested. Details on the items of the questionnaire are given in the *Online Supplementary Table S3*.

Altogether, 55 specific comorbidities in nine categories or syndromes were addressed. In addition, physicians had the opportunity to add text comments. The completed questionnaires were sent to the GMALL study center and information was collected in a database. In case of erroneously documented symptoms in the category of GvHD in patients without prior allogeneic SCT, the comorbidities were allocated to the respective organ categories. In case of documentation by both hospital physician and general practitioners, data were combined, and potential discrepancies clarified.

Study endpoints

The study was designed to analyze frequencies and severity of comorbidities and syndromes. In order to analyze the potential impact of patient or treatment-related factors on these outcomes, two major endpoints were analyzed: (i) general comorbidity status defined as occurrence of at least one comorbidity in nine organ categories or specific syndromes *versus* occurrence of no comorbidity and (ii) ECOG status of 0-1 compared to 2-4. Furthermore, the correlation of these factors with distinct comorbidities or syndromes was described. Four relevant patient or disease related factors were defined: sex, age at ALL diagnosis (15-55 years *vs.* 56-65 years), history of any SCT *versus* no SCT and finally the study cohorts were grouped by overall (02/84-05/93 *vs*. 06/99-07/03).

Statistical analysis

Statistical analysis was performed by SAS proprietary software Release 9.4. Patient characteristics and incidences of comorbidities or syndromes were described by calculating absolute frequencies, median and range in comparison of different patient and treatment characteristics. The impact of patient and treatment characteristics as predictive factors for outcome parameters was analyzed in univariate analysis (χ^2-test or bidirectional Fisher's exact test) and multivariate analysis by logistic regression. For logistic regression, the effect of SCT, age in two groups (≤ or > 55 years), and sex was analyzed. As significance level for univariate and multivariate analysis α=5% was chosen.

Results

Study population and patient characteristics

Overall, 1,413 long-term survivors were identified in the databases of GMALL trials 02/84-07/03. Patients with a follow-up of less than 3 years at time point of data collection (n=12) were excluded. One hundred and twenty-two patients, mostly from trials 06/99 and 07/03 with a follow-up of 3-4 years (n=41) or 4-5 years (n=76) were included. Six hundred and ten completed questionnaires on 561 patients were collected. There was no difference in terms of major clinical characteristics between patients with available questionnaire and those without (*Online Supplementary Table S1*). Five hundred and eighty-four questionnaires from 538 patients were eligible (Table 1). This included 295 patients documented by physicians from hospitals, 197 patients documented by practitioners and 46 cases with responses from both sources. Data were collected from trials 02/84 (n=41), 03/87 (n=16), 04/89 (n=60), 05/93 (n=180), 06/99 (n=162), 07/03 (n=79).

Median age at diagnosis was 29 (range, 15-64) years and did not vary between studies (Table 1). Fourty patients had experienced a relapse during their medical history. Fourty-nine patients had Ph/BCR-ABL-positive ALL. At diagnosis 36% of the patients were younger than 25 years (n=191) and 5% older than 55 years (n=26). The median age at time of follow-up was 39 (range, 19-74) years.

The median follow-up was 7.5 (range, 3-24) years. Most patients (78%) were alive more than 5 years from diagnosis (n=416) including 35% with more than 10 years follow-up.

Overall, 31% (n=168) of the patients had received SCT; of these 88% were allogeneic SCT (n=147) and 12% were autologous SCT (n=21). The proportion of patients with any SCT increased over time, from 14% in studies 02/84-04/89 to 21% in study 05/93 to 47% in studies 06/99-07/03 (Table 1). Seventy-three percent of the transplanted patients had a follow-up of 4 or more years after transplantation.

General condition

Five hundred and twenty-two patients were evaluable for their ECOG performance status. No restrictions (ECOG=0)

were documented for 70% of the patients (n=367). Twenty-four % (n=125) of the patients had slight restrictions (ECOG 1). More relevant restrictions (ECOG 2-4) were present in 6% of the patients (n=30). *Online Supplementary Table S4* gives the frequencies of ECOG status by age groups and trial generation.

Overall incidences of comorbidities and specific syndromes

For one third of survivors of ALL no comorbidities were reported. About 66% had developed some comorbidity (n=355). Comorbidities most frequently involved the neurological system (27%), the endocrine system (17% of male and 24% female patients) and skin including alopecia (18%) (Table 2). For 37 items, a grading according to CTCAE had been requested and 692 events had been classified. Overall, the median of severity grade according to CTCAE was 2 (range, 1-4). Higher severity grades 3 and 4 were documented in the neurologic system (n=62), in specific syndromes (n=59), in the cardiac system (n=26), in lung (n=28), and in eye impairment (n=21).

Incidences and characteristics of specific syndromes

GvHD: the most frequently documented specific syndrome was GvHD in 15% (n=79) overall (Table 2) and 47% of the patients with SCT. GvHD was manifested by skin involvement (n=52), eye impairment/sicca syndrome (n=45), liver affection (n=25), intestine (n=12), or lung (n=10). Half of the patients with GvHD had only one organ involved, but in 30% and 19% two or more organs were involved, respectively. The median time from primary diagnosis to GvHD documentation was 3 (range, 0.2-8) years.

Osteonecrosis: osteonecrosis was documented in 8% (n=41). The incidence was 10% in female and 6% in male patients respectively (Table 3). The hip (n=18), shoulder (n=8) or both large joints (n=2) were involved. The severity was grade 1-2 in 18% of osteonecrosis cases (n=7), grade 3 in 48% (n=19), grade 4 in 35% (n=14), and unknown in 2% (n=1). The incidence was 9% in transplanted and 7% in non-transplanted patients (P>0.05). The median age was 24 (range, 15-72) years at diagnosis of ALL and 27 (range, 18-59) years at the event. The median time from ALL diagnosis to event was three (range, 0-13) years (*Online Supplementary Table S5*). The incidence of grade 3/4 cases in adolescent patients was 13% and 5% in adults, respectively (*Online Supplementary Table S5*).

Secondary malignancies: second malignancies were reported in 4% (n=21). The median age at primary diagnosis was 36 (range, 16-64) years and the median age at event was 46 (range, 22-72) years. The median time from diag-

Table 1. Data collection, patient and treatment characteristics.

Chracteristics	Study Cohort			
	Trials 02-04	Trial 05	Trials 06-07	Total
Evaluable patients, N	117	180	241	538
From hospitals, N (%)	27 (23)	79 (44)	189 (78)	295 (55)
From private practitioners, N (%)	79 (68)	77 (43)	41 (17)	197 (37)
From both, N (%)	11 (9)	24 (13)	11 (5)	46 (8)
Male, N (%)	65 (56)	111 (62)	151 (63)	327 (61)
Female, N (%)	52 (44)	69 (38)	90 (37)	211 (39)
Age in yrs at diagnosis, median	28	29	30	29
Age in yrs at diagnosis, range	15-60	15-64	15-64	15-64
≤ 25 years, N (%)	44 (38)	66 (37)	81 (34)	191 (36)
26-55 years, N (%)	70 (60)	104 (58)	147 (61)	321 (60)
> 55 years, N (%)	3 (2)	10 (5)	13(5)	26 (5)
Age in yrs at evaluation, median	46	38	36	39
Age in yrs at evaluation, range	22-72	20-74	19-69	19-74
≤ 25, N (%)	1 (1)	7 (4)	42 (17)	50 (10)
> 25-55, N (%)	85 (73)	142 (76)	173 (72)	400 (74)
> 55, N (%)	31 (26)	31 (17)	26 (11)	88 (16)
Follow-up ≤ 7.5 yrs, N (%)	1 (1)	28 (16)	240 (99)	269 (50)
Time since diagnosis, evaluation in yrs, median	16.5	9	5	7
Time since diagnosis, evaluation in yrs, range	3-24	4-14	3-8	3-24
Stem cell transplantation, N (%)	16 (14)	38 (21)	114 (47)	168
Chemotherapy alone, N (%)	101 (86)	142 (79)	127 (53)	370

yrs: years.

nosis of ALL to diagnosis of secondary malignancy was 11 (range, 2-23) years. The detected tumors were melanoma (n=4), basal cell carcinoma (n=4), hematological malignancies (n=4), breast cancer (n=2), prostate cancer (n=2), glioblastoma, small intestine cancer, cancers of stomach, and cervix, as well as sarcoma (each n=1). The incidence of secondary malignancy was similar in transplanted and non-transplanted patients (*Online Supplementary Table S6*).

Fatigue was observed in 13% (n=71). Most patients developed minor grades (1-2) (n=63) whereas seven and one patient developed grade 3 or 4, respectively. The median age at diagnosis of ALL was 29 (range, 15-64) years and the median age at event was 35 (range, 18-67) years. The median time from primary diagnosis to fatigue event was 3.5 (range, 0,1-17 years). The incidence of fatigue was 19% in transplanted and 11% in non-transplanted patients (P>0.05). The incidence of grade 3/4 in adolescents was 1% *versus* 2% in adult patients (P>0.05) (*Online Supplementary Table S5*).

Other specific syndromes: infections in the past 12 months, mainly with respiratory involvement, were described in 12% of the patients. Hypothyroidism was seen in 5% of patients (n=26), hyperthyroidism in 1% (n=7).

Incidences and characteristics of comorbidities according to organ classes

Neurologic disorders: 27% of the patients developed neurologic disorders (Table 2). Seventy-one patients (13%) had mood alterations (grade 3 in n=15). Cognitive disturbances or memory alterations were documented in 7%. Polyneuropathy was documented in 7% (n=35; grade 3 in n=14) including peripheral sensory and/or motor neuropathy. In addition, sensory or motor/reflex impairment as distinct comorbidities were documented in further 28 patients (n=11 and n=17, respectively), accounting for a total incidence of peripheral nerve disorders of 12%. Leukoencephalopathy was documented in 16 patients (3%). Fourty-two percent of these patients had received a prior SCT.

Endocrine disorders: 20% of the patients developed some disorder in the endocrine system (n=105). The overall incidence was 24% for women and 17% for men. Infertility in females was adjusted for age and described in 17% of the female patients younger than 40 years at time of evaluation (n=18/104). Six percent of the female patients had osteoporosis (n=12). Four percent of the male patients had documented infertility (n=12) and additional eight patients had a pathological hormone status and/or erectile dysfunction, but without documentation of infertility. Diabetes was documented in 5% of female and 2% of male patients.

Skin disorders: 18% (n=97) of the patients developed skin impairment. Alopecia was the most common finding (10%) and 13 had documented skin GvHD in addition.

Ocular disorders: eye impairment was documented for 12% of the patients (n=65). The most frequent ocular comorbidity was cataract in 6% (n=30; grade 3 in n=16). Four percent had conjunctivitis and 3% had visual impairment. Sicca syndrome, documented as part of GvHD, was highly correlated with documentation of further eye impairment (P<0.0001).

Other organ categories: the incidences of diseases in other organ systems are summarized in Table 2. Patients developed cardiac diseases (13%), e.g., hypertension (9%); liver or kidney diseases (10%), e.g., liver failure (6%); lung diseases (8%), e.g., dyspnea (5%); or diseases of the gastrointestinal system (6%).

Predictive factors for long-term general condition and occurrence of comorbidities

General condition: 98% of patients without SCT compared to 86% of SCT patients had an ECOG status of 0-1 (P<0.0001). Ninety-five percent of the patients younger and 84% of those older than 55 years at time of diagnosis had no or minor restrictions of general condition (P=0.02). If younger patients (≤55 years) were subdivided at a cut-off of 25 years, the incidences of ECOG status 0-1 were 96% and 94%, respectively (P>0.05). No differences for ECOG status were evident regarding the trial cohorts, or

Table 2. Overall incidences of comorbidities and specific syndromes.

Incidences	Comorbidity		Evaluable per item
	N	%	N
No comorbidity	355	66	538
Comorbidities according to organ classes			
Skin	97	18	538
Lung	41	8	538
Cardiac system	70	13	538
Gastrointestinal system	30	6	537
Neurologic system	147	27	538
Kidney/liver	56	10	538
Eyes	65	12	537
Endocrine system			
Women	50	24	211
Men	55	17	327
Specific syndromes			
Infection (in past 12 months)	64	12	533
Fatigue	71	13	533
GvHD	79	15	538
Osteonecrosis	41	8	538
Secondary malignancy	21	4	538
Hypothyreodism	26	5	537
Hyperthyreodism	7	1	538

GvHD: graft-*versus*-host disease.

Table 3. Predictive factors for general condition and incidence of comorbidities.

	SCT *vs.* CT					Sex					Age at diagnosis					Study Cohort				
	SCT		CT alone			male		female			≤55 years		>55 years			Trial 2-4		Trial 5-7		
	N	%	N	%	*P* uni (multi)	N	%	N	%	*P* uni (multi)	N	%	N	%	*P* uni (multi)	N	%	N	%	*P* uni (multi)
ECOG grade 0-1	142	86	350	98	<0.0001 (<0.00001)	297	94	195	95	ns	471	95	21	84	0.02 (0.02)	109	96	383	94	ns (ns)
≥ one comorbidity	146	87	209	57	<0.0001 (<0.0001)	204	62	151	72	0.03 (ns)	335	65	20	77	ns (ns)	83	71	272	65	ns (0.007)
Skin	53	32	44	12	<0.0001 (<0.0001)	49	15	48	23	0.0222 (0.0283)	92	18	5	19	ns (ns)	17	15	80	19	ns (ns)
Lung	30	18	11	3	<0.0001 (<0.0001)	29	9	12	6	ns (ns)	39	8	2	8	ns (ns)	5	4	36	9	ns (ns)
Cardiac system	27	16	43	12	ns (0.03)	41	13	29	14	ns (ns)	63	12	7	27	0.03 (0.02)	24	21	46	11	0.006 (0.0012)
GI system	15	9	15	4	0.02 (0.02)	22	7	8	4	ns (ns)	27	5	3	12	ns (ns)	5	4	25	6	ns (ns)
Neurologic system	61	36	86	23	0.001 (0.002)	77	24	70	33	0.014 (0.02)	136	27	11	42	ns (ns)	36	31	111	26	ns (ns)
Kidney/liver	39	23	17	5	<0.0001 (<0.0001)	33	10	23	11	ns (ns)	51	10	5	19	ns (ns)	8	7	48	11	ns (ns)
Endocrine system (f)	26	38	24	17	0.0009 (0.0011)	-	-	50	24	-	47	23	3	33	ns (ns)	8	15	42	26	ns (ns)
Endocrine system (m)	34	34	21	9	<0.0001 (<0.0001)	55	17	-	-	-	49	16	6	35	0.04 (0.0177)	8	12	47	18	ns (ns)
Eye impairment	48	29	17	5	<0.0001 (<0.0001)	36	11	29	14	ns (ns)	59	12	6	23	ns (0.04)	10	9	55	13	ns (ns)
Infection	34	20	30	8	<0.0001 (0.0001)	29	9	35	17	0.008 (0.01)	61	12	3	12	ns (ns)	13	11	51	12	ns (ns)
Fatigue	32	19	39	11	0.006 (0.007)	40	12	31	15	ns (ns)	67	13	4	15	ns (ns)	11	9	60	14	ns (ns)
GvHD	79	47	0	0	<0.0001 (ns)	46	14	33	16	ns (ns)	75	15	4	15	ns (ns)	2	2	77	18	<0.0001 (0.0004)
Osteonecrosis	15	9	26	7	ns (ns)	20	6	21	10	ns (ns)	41	8	0	0	ns (ns)	12	10	29	7	ns (ns)
Secondary malignancies	6	4	15	4	ns (ns)	14	4	7	3	ns (ns)	18	4	3	12	0.04 (0.03)	10	9	11	3	0.003 (0.003)
Hypothyroidism	10	6	16	4	ns (ns)	11	3	15	7	ns (ns)	26	5	0	0	ns (ns)	5	4	21	5	ns (ns)
Hyperthyroidism	2	1	5	1	ns (ns)	4	2	3	1	ns (ns)	7	1	0	0	ns (ns)	2	2	5	1	ns (ns)

SCT: stem cell transplantation; CH: chemotherapy; ns: not significant >0.05; GI: gastrointestinal; GvHD: graft-*versus*-host disease; *P* uni: *P* value for univariate analysis; multi: *P* value for multivariate analysis; f: female; m: male.

sex (Table 3). In a multivariate analysis the significant effect of SCT (P<0.001) and age ≤ or > 55 years (P=0.02) on ECOG status was confirmed.

Overall incidence of any comorbidity: the incidence of any comorbidity was 87% in patients with SCT compared to 57% in those without SCT (P<0.0001). Females showed a slightly higher incidence of any comorbidity (72% *vs*. 62%; P=0.03). Older patients had a higher incidence of comorbidities (77%) compared to younger patients (65%), but the difference was not significant (P=0.05). The significant impact of SCT was confirmed in a multivariate analysis. The trial cohort had a significant impact on the occurrence of comorbidities in the multivariate approach only (P<0.007) (Table 3).

Incidence of specific comorbidities: in univariate analysis, SCT had a significant impact on the incidence on nearly all comorbidities except for cardiac diseases; this was confirmed in multivariate analyses (Table 3). Sex had a significant effect only on neurologic disorders with incidences of 33% in females compared to 24% in males (P=0.01). Skin comorbidity was described more often in female patients (23% *vs*. 15%) (P=0.02). Age at diagnosis was correlated to cardiac disorders, which were described in 12% of the patients younger and 27% of the patients older than 55 years (P=0.03). Age was also correlated to the occurrence of endocrine disorders in male patients (16% *vs*. 35%) (P=0.04) (Table 3).

Incidence of specific syndromes: patients with SCT had significantly higher incidences of GvHD (46% *vs*. 0%; P<0.0001), infections within the last 12 months (20% *vs*. 8%; P<0.0001), and fatigue (19% *vs*. 11%; P=0.007). No impact of SCT was seen for secondary malignancies, osteonecrosis, and hyper- or hypothyroidism (Table 3).

Sex correlated with the incidence of infections (17% *vs*. 9% in females and males; P=0.008). Age had an impact on secondary malignancies (4% in younger and 12% in older patients; P=0.04). Trial cohort was correlated to occurrence of GvHD, which was observed in 18% of the recent compared to 2% in the historic trials (P<0.0001). Conversely, the incidence of secondary malignancies was higher in the historic trials (9%) compared to the recent ones (3%) (P=0.003). The described differences were also confirmed in multivariate analysis.

Further correlation of age at different cut-offs to ECOG status and incidence of comorbidities is reported in the *Online Supplementary Table S7*.

Discussion

Numerous studies have been conducted in long-term survivors of pediatric cancer including ALL (reviewed in [8]). They reported a higher mortality, more chronic medical conditions, impaired general and mental health, functional impairment, and poorer social parameters compared to healthy relatives and the general population.[5] After treatment modifications, the number of late effects was lower in patients treated with contemporary regimens. However, ALL survivors still displayed an increased risk of chronic medical conditions compared to healthy siblings.[7]

The use of intensified pediatric-based chemotherapy contributed to improved outcome in younger adults. However, in many study groups for adult ALL up to 50% of patients are considered at high-risk for relapse with an indication for allogeneic SCT. Despite an increasing number of long-term survivors of adult ALL, little is known about the health status of cured patients.

To our knowledge, this report covers the largest number of adults with ALL analyzed with a systematic approach to describe the health condition of long-term survivors. Due to the infrastructure of the GMALL study group it was possible to identify physicians involved in aftercare and to collect the respective documentation. The data represent a comprehensive and structured summary of standard aftercare source data documentations. It might be a potential limitation of the study, that aftercare was split between hospitals and practitioners. Also, the comparison to patients' self-assessment would be of interest.

All patients had received pediatric-based chemotherapy; cranial irradiation and intrathecal therapy were part of all trials. Treatment intensity increased in subsequent trials. Particularly, more patients became candidates for SCT, mostly with total body irradiation as conditioning regimen. Given these facts, it is of interest that in total 94% of the patients had no (ECOG=0) or only slight restrictions (ECOG=1) in the general condition. Even in the more intensive recent trials the general condition of ALL survivors was generally good. Not surprisingly, older patients had a higher risk to develop restrictions of the ECOG, whereas this risk was low in patients with ALL diagnosis in young adulthood.

Two thirds of patients had developed a significant disease documented in aftercare at a median age of 39 years. The study does not allow comparison of disease incidence with the general population mainly due to the lack of incidence data from comparable general population cohorts. Altogether, the incidence of general comorbidities like cardiovascular diseases, gastrointestinal or lung diseases was rather moderate in the study population.

On the other hand, the incidence of certain comorbidities with probable relationship to previous ALL therapy was quite high such as cognitive and psychiatric disorders (27%). Childhood ALL survivors showed an increased risk for neurologic dysfunction compared to siblings.[5] This was in the past mainly attributed to the effects of cranial irradiation[15] or HD methotrexate.[16] The developing brain may be more prone to damages induced by cranial radiotherapy but also adult ALL survivors often complain about dis-

turbed concentration or memory. For "chemo-brain", a physiological correlate is unknown.[17] It is difficult to measure complaints in a reproducible and quantifiable way. Potential tests which are applicable with limited effort in general practice, as the DemTect test,[18] may not be sensitive enough. More differentiated tests as those developed for pediatric ALL should therefore be used in adults as well.[19] Since in our study most patients had received prophylactic cranial irradiation it remains open, whether the incidence of neurologic dysfunction would be lower with approaches without irradiation. The GMALL study group performed a randomization between cranial irradiation with intrathecal prophylaxis and intrathecal prophylaxis only. This trial will hopefully answer some of the open questions.

Similar considerations apply to fatigue, as observed in 13% of adult ALL survivors in our study. A relevant incidence of fatigue was also reported by others.[20] The syndrome can present many years after therapy and may be associated with depression and reduced quality of life. So far, it seems that fatigue is only rarely diagnosed by physicians involved in aftercare.[21] The prevention of fatigue and its detection by specific questionnaires should therefore be one focus of aftercare.

A significant number of patients had endocrine disorders, including infertility, osteoporosis, and diabetes mellitus. The detection of infertility raises methodological problems. It is known that patients can maintain fertility after chemotherapy,[22] whereas infertility is observed in most SCT patients.[23,24] In the absence of systematic testing, infertility is usually only detected in patients in childbearing age and with the desire to have children. According to a patient questionnaire, this is the case in less than 50% of the former ALL patients (NG, personal communication). Despite these limitations, from the patient's perspective, our data are still of interest, with 18% infertility documented in women and 12% infertility in men.

Avascular osteonecrosis is a clinically relevant problem particularly observed in younger adults.[25-27] Risk factors are intensified treatment with steroids and these effects may be enhanced by asparaginase or HD methotrexate. It is difficult to compare incidences between trials since protocols, detection methods, and observation periods vary. In one pediatric study with postinduction dexamethasone or prednisone pulses the incidence of skeletal toxicity was 13%. It was higher (25% *vs*. 11%) in older children (>10 years *vs*. <10 years) treated with dexamethasone pulses.[26,27] In contrast the UKALL/ECOG2993 study for adult ALL found an overall incidence of 4% osteonecrosis. The incidence was higher in younger (<20 years) *versus* older patients.[28] In our analysis, overall, 8% of the patients developed osteonecrosis, mostly grade 3-4 and with a significantly higher incidence in younger patients. No incidence increase was observed in the more recent trial cohorts and SCT had no significant impact. The incidence may be underestimated, since only long-term survivors were analyzed. Due to the potential longer latency period and the correlation with osteoporosis occurring at higher age, a close observation of this complication should be considered for future ALL trials.[29]

Survivors of pediatric ALL have an additional risk to develop cancer resulting e.g., from the cell damage induced by chemotherapy and/or irradiation.[30] In our study, the risk of secondary malignancies was higher in older patients and with longer follow-up. Published data show a variety of solid tumors.[31] For these malignancies a lifetime increase can be observed. Of interest, in our study only one secondary CNS tumor was observed, although most patients had received cranial irradiation per protocol. This is a significant difference compared to childhood ALL cohorts.[32]

The frequent second malignancies are hematologic neoplasias, which mostly occur within the first 5-10 years after end of chemotherapy.[33] These malignancies (n=4) may be underestimated in our cohort, since only long-term survivors were analyzed whereas patients with secondary hematologic malignancies may already die early.[31,32] Our observations underline that aftercare should have a specific focus on skin tumors and breast cancer. Assessment of the real incidence of secondary malignancies, would require a prospective trial addressing this question. Interestingly the experience of SCT apparently did not affect the risk of secondary malignancies.

Overall, SCT was the most prominent risk factor for restrictions of general condition as well as for specific comorbidities or syndromes. Specific late effects such as skin disorders correlated to GvHD, sicca syndrome, restrictive and obstructive pulmonary disorders and cataract have been described by others.[34,35] Of note, many SCT patients in our cohort (47%) showed symptoms of GvHD and significantly more skin and eye disorders, neurologic symptoms or fatigue were observed. The extent of morbidity after SCT may even be underestimated since patients dying early are not included in this analysis.

Overall, the study provided important insights in the spectrum of potential late effects of disease and treatment in cured ALL patients. It does not show the total treatment-related burden of morbidity and mortality. Nevertheless, these data are helpful to inform physicians in aftercare. Therefore, the GMALL study group developed a patient card with information summarizing the ALL treatment, information on time points of aftercare evaluations including recommended questionnaires and laboratory or physical examinations. Academic clinical trials are usually funded by public agencies and no funds are available for the long-term follow-up. This would be essential to improve patient care and to completely evaluate standard and new treatment approaches. The

outcomes may change with more intensive chemotherapy regimens and/or optimized conditioning regimens or approaches to manage GvHD. In order to provide the full picture of treatment-related burden, for future studies a prospective, standardized set of follow-up tests and respective documentations would be desirable and part of long-term observation of clinical trial patients. To this end, our trial provides reference data for these patient-centered endpoints, which are of increasing importance also for the evaluation of new targeted therapy approaches in *de novo* ALL.

Disclosures

No conflicts of interest to disclose.

Contributions

NG designed the analysis. NG and KI performed the analysis. All authors recruited patients, conducted patient follow-up, and collected clinical data. The manuscript was prepared by NG and KI and all authors participated in data interpretation and drafting of the manuscript and read, revised, and approved the final manuscript.

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Data-sharing statement

All data generated or analyzed during this study are included in this published article (and its Online Supplementary Appendix).

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