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A population-based study of 135 lymphomas after solid organ transplantation: The role of Epstein-Barr virus, hepatitis C and diffuse large B-cell lymphoma subtype in clinical presentation and survival

AMELIE KINCH[1], EVA BAECKLUND[2], CARIN BACKLIN[2], TOR EKMAN[3], DANIEL MOLIN[4], GUNNAR TUFVESON[5], PIA FERNBERG[6], CHRISTER SUNDSTRÖM[7], KARLIS PAUKSENS[1] & GUNILLA ENBLAD[4]

[1]*Department of Medical Sciences, Section of Infectious Diseases, Uppsala University, Uppsala, Sweden,* [2]*Department of Medical Sciences, Section of Rheumatology, Uppsala University, Uppsala, Sweden,* [3]*Department of Oncology, Karolinska University Hospital, Stockholm, Sweden,* [4]*Department of Radiology, Oncology and Radiation Sciences, Section of Oncology, Uppsala University, Uppsala, Sweden,* [5]*Department of Surgical Sciences, Uppsala University, Uppsala, Sweden,* [6]*Department of Anaesthesiology and Intensive Care, Karolinska University Hospital, Stockholm, Sweden and* [7]*Department of Immunology, Genetics and Pathology, Uppsala University, Uppsala, Sweden*

Abstract

Background. Epstein-Barr virus (EBV) plays a major role in the development of post-transplant lymphoproliferative disorder (PTLD), but there is an increasing awareness of EBV-negative PTLD. The clinical presentation of EBV-negative PTLD has not been as well characterised as EBV-positive cases. Further, there is limited knowledge on the clinical importance of diffuse large B-cell lymphoma (DLBCL) cell of origin subtype post-transplant. *Materials and methods.* We studied the role of EBV, hepatitis C (HCV) and DLBCL subtype in clinical presentation and survival in 135 post-transplant lymphomas diagnosed 1980–2006 in a population-based cohort of 10 010 Swedish solid organ transplant recipients. The lymphomas were re-evaluated according to WHO 2008, examined for EBV, and clinical data were collected from medical records. *Results.* Lymphoma incidence rate was 159/100 000 person-years and is also reported by lymphoma subtype. EBV-negative lymphomas constituted 48% and were associated with HCV infection ($p = 0.02$), bone marrow involvement ($p < 0.001$), and T-cell phenotype ($p = 0.002$). Among DLBCL, 78% were of non-germinal centre subtype, which was associated with EBV-positivity (69%, $p = 0.001$), early occurrence ($p = 0.03$), heart/liver/lung/pancreas recipients ($p = 0.02$), anti-T-cell globulin ($p = 0.001$), and tacrolimus treatment ($p = 0.02$). DLBCL subtypes had similar overall survival. Five-year overall survival was 42% in all treated patients. Independent poor prognostic factors were older age, B symptoms, ECOG 2-4, kidney/pancreas/heart recipients, T-cell lymphoma, and HCV-infection. *Conclusions.* With long follow-up, a large part of PTLD is EBV-negative, due to a high proportion of T-cell lymphomas and low of polymorphic PTLD. EBV-negative PTLD have a different clinical presentation. HCV may play an aetiological role in late-onset PTLD and was revealed as a new prognostic factor for inferior survival that needs to be confirmed in larger studies. The heavier immunosuppression in non-kidney transplantations seems to play a role in the development of non-germinal centre DLBCL. DLBCL cell of origin subtype lacks prognostic importance in the transplant setting.

Patients undergoing solid organ transplantation (SOT) have an approximately 10-fold increased risk to develop lymphoma compared with the general population, with higher risk in non-kidney recipients, during the first year following SOT, and at five years post-transplant and onwards [1–4]. Post-transplantation lymphoproliferative disorder (PTLD) is a heterogeneous group of lymphoid lesions ranging from early lesions and polymorphic PTLD to monomorphic lymphomas and classical Hodgkin lymphomas [5].

Correspondence: A. Kinch, Department of Medical Sciences, Section of Infectious Diseases, Uppsala University, 751 85 Uppsala, Sweden. Tel: +46 186115655. Fax: +46 186115631. E-mail: amelie.kinch@medsci.uu.se

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Epstein-Barr virus (EBV) plays a critical role in the development of PTLD following SOT, with 60–70% reported to be EBV-positive [5]. Early-onset PTLD (< one year post-transplant) is more frequently EBV-positive and is associated with young age, EBV seronegativity pre-transplant, and allograft involvement [4,6]. Older age is a risk factor for late-onset PTLD, which is more often monomorphic and EBV-negative [4,5,7]. Other reported risk factors are the intensity of immunosuppression and type of organ transplantation [1,2,8]. EBV-negative PTLD have a different aetiology and clinical presentation that is not fully investigated.

A small number of studies indicate that the majority of diffuse large B-cell lymphomas (DLBCL) after SOT, in contrast to the general population, are of the non-germinal centre (non-GC) cell of origin subtype [9,10]. The germinal centre (GC) subtype is associated with a better prognosis in immunocompetent patients, but correlation with survival in the transplant setting has not been reported [9].

The aim of this study was, in a population-based cohort of lymphomas after SOT gathered from the entire Swedish population between 1980 and 2006, to re-evaluate the lymphomas according to the 2008 WHO classification and specifically study the differences in clinical presentation and outcome between EBV-positive and -negative lymphomas. Indolent lymphomas were included although they are not defined as PTLDs according to the WHO classification. Furthermore, we studied the proportion of DLBCL cell of origin subtypes and their association to EBV and the clinical presentation. Finally, we identified prognostic factors for overall survival.

Material and methods

Registers

From the Swedish National Inpatient Register, which contains individual-based information on all patients receiving inpatient care in Sweden, we identified all patients discharged after SOT between 1 January 1970 and 31 December 2006 (n = 10 010, representing 85 015 person-years). Through linkage with the Swedish Cancer Register, to which it is compulsory for every clinician and pathologist to report any incident cancer, we identified 145 reported cases of lymphoma after SOT between 1 January 1980 and 31 December 2006. Between 1970 and 1980 only two cases of PTLD were reported to the cancer register, and these were not included. Lymphomas were defined according to the ICD 7 codes 200, 201, 202 and 204.1. Plasma cell tumours were not included in the study. The study was approved by the Regional Ethical Review Board in Uppsala, Sweden.

Study population

Of the initial 145 reported cases, the study included 135 individuals (10 children < 18 years and 125 adults), among whom seven adults were diagnosed at autopsy. Ten cases were excluded because of not having undergone SOT (n = 2), lymphoma existed pre-transplant (n = 2), or inability to confirm pathology (n = 6). A total of 122 cases had sufficient material for lymphoma re-evaluation and in 13 cases re-evaluation could not be done due to missing histological material, but these cases were not excluded since the original pathology reports and medical records unequivocally supported the lymphoma diagnosis.

Detailed information about the patients was retrieved retrospectively from the medical records from all four transplantation centres in Sweden (Göteborg, Stockholm, Uppsala, Malmö/Lund), as well as from the hospitals where the patients were followed post-transplant. Performance status according to Eastern Cooperative Oncology Group (ECOG), staging according to Ann Arbor, and age-adjusted International Prognostic Index (aaIPI), were registered retrospectively when possible, if not documented in the medical records.

Time to lymphoma was defined as time from the first transplantation where the allograft remained in the body to lymphoma diagnosis. Date for first transplantation was used instead in two patients without allograft at lymphoma diagnosis.

Re-evaluation of lymphomas/PTLDs and analysis of EBV in tissue

Re-evaluation of the tumour biopsies according to the 2008 WHO classification of lymphoma [5] was made by an experienced haematopathologist (CS). Indolent B-cell lymphomas are not defined as PTLDs but were included since the aim was to study all lymphomas and early forms of PTLD occurring post-transplant. DLBCL were classified as either GC or non-GC subtype according to the Hans algorithm using CD10, bcl-6 and IRF-4 antibodies [11]. We analysed presence of EBV in lymphoma sections using EBV-encoded RNA (EBER) in situ hybridisation (n = 109). In cases with scarce material, the EBER status in the original pathology report was used (n = 3), or if there was a positive result for latent membrane protein-1 (LMP-1) the lymphoma was considered EBV-positive (n = 7).

Statistical analysis

χ^2 or Fisher's exact test (if < 5 observations) was applied for categorical variables, and Mann-Whitney U-test for continuous variables. Overall survival was

defined as time from lymphoma diagnosis until death. Seven patients who were diagnosed at autopsy were excluded from survival analysis. Survival curves were generated using the Kaplan-Meier method and differences were calculated using the log-rank test. Multivariate analysis was performed using the Cox proportional hazards regression model. P-values <0.05 were considered statistically significant. All statistical analyses were performed using Statistica software (version 11, Stat Soft Inc.).

Results

Baseline characteristics, incidence, and lymphoma/PTLD subtypes

Table I shows the baseline characteristics of the study population. The median follow-up time regarding clinical data for the cohort was 9.2 years (range 0.2–33) from transplantation until death or last clinical control. All surviving patients were followed at least six years. The incidence rate of lymphoma was 159 per 100 000 person-years among transplant recipients and is reported by lymphoma subtype in Table II.

The distribution of lymphoma/PTLD subtypes was as follows; 63% monomorphic B-cell lymphoma, 13% T-cell lymphoma, 6% polymorphic PTLD, 4% Hodgkin lymphoma, 1% early lesion, and 7% indolent B-cell lymphoma (Table II). The most common subtype was DLBCL (40%). Median time to lymphoma was 4.3 years (range 0.1–26); 28% were early-onset and 21% very late-onset (>10 years post-transplant) (Table III). Polymorphic PTLD presented earliest post-transplant (median 1.5 years), followed by monomorphic B- and T-cell lymphomas at median 4–6 years, and Hodgkin lymphomas developed late (median 9.5 years).

Extranodal disease was found in 79% (Table III). The lymphoma was frequently located in the allograft (19%) or in organs near the graft. Gastrointestinal tract involvement was more common in recipients of abdominal organs than of heart and lung ($p=0.02$). Lung recipients were more likely to have allograft involvement, 68% versus 10% ($p<0.001$).

EBV-positive versus -negative lymphoma/PTLD

EBV-status was determined in 88% of the lymphomas (Table II). Overall, 62 (52%) of the lymphomas were EBV-positive, 55 by EBER and seven by LMP-1. All early lesions, polymorphic PTLD and Hodgkin lymphomas were EBV-positive. Aggressive B-cell lymphomas were more frequently EBV-positive as compared with indolent B-cell lymphomas, 57% versus 11% ($p=0.01$), and T-cell lymphomas, 57% versus 12% ($p<0.001$).

Table I. Baseline characteristics of the study population.

	Median (range) or n (%)
Follow-up[1], years	
All (n = 135)	9.2 (0.2–33)
Surviving patients (n = 27)	9.3 (6–18)
Age at first transplantation, years	47 (0.7–72)
Age < 18 years	10 (7.4)
Age > 18 years	125 (92.6)
Transplant type	
Kidney	73 (54)
Heart	21 (16)
Liver	19 (14)
Lung	19 (14)
Kidney + pancreas	3 (2)
Kidney donor type, living	22 (29)
Dialysis pre-transplant	63 (83)
Other malignancies than lymphoma	
Pre-transplant[2]	3 (2)
Post-transplant before lymphoma[3]	5 (4)
Immunosuppressive regimen	
Corticosteroids	135 (100)
Cyclosporine A	117 (87)
Azathioprine	106 (79)
ATG[4]	55 (42)
Mycophenolic acid	30 (22)
Tacrolimus	28 (21)
Anti CD-3	15 (11)
Sirolimus	1 (0.7)
Other	11 (8)
Rejection episodes	
Acute before lymphoma	77 (57)
Chronic before lymphoma	19 (14)
Graft failure	
Never	87 (64)
Yes, before lymphoma	24 (18)
Yes, after lymphoma	28 (22)
Retransplantation	
Before lymphoma[5]	15 (11)
After lymphoma	8 (6)
Diagnosis at autopsy	7 (5)
Calendar year of transplantation	
1970–1979	8 (6)
1980–1989	36 (27)
1990–1999	76 (56)
2000–2006	15 (11)
Calendar year of lymphoma	
1980–1989	11 (8)
1990–1999	59 (44)
2000–2006	65 (48)

[1]From transplantation to death or last clinical control; [2]One hepatocellular carcinoma and one cholangiocarcinoma that were diagnosed in the removed liver at transplantation and one cured uterine cancer. The cholangiocarcinoma was not radically excised and the patient died of relapse of the carcinoma; [3]Three cutaneous squamous-cell carcinoma, one neuroendocrine tumour and one adenocarcinoma of the colon; [4]Missing data in four cases; [5]In the second transplantation 12 patients received a kidney and three patients multiple organs. Two individuals received a kidney in their third transplantation. ATG, anti-T-cell globulin.

EBV-positive lymphomas developed earlier post-transplant, median 2.1 versus 6.7 years ($p<0.001$), were associated with early-onset, 39% versus 14% ($p=0.002$), and occurred at a younger

Table II. Distribution of post-transplant lymphoma/PTLD subtypes according to the 2008 WHO classification, overall and by EBV-status in lymphoma tissue (by EBER or LMP-1), and incidence rate per 100 000 person-years for lymphoma subtypes.

Lymphoma/PTLD subtype	All n (%)	Available EBV data, n (%)	EBV+ n (%)	EBV- n (%)	Incidence rate/ 100 000 PY
All	135	119 (88)	62 (52)	57 (48)	159
Early lesion	2 (1.5)	2	2 (100)	0	
Plasmacytic hyperplasia[1]	1 (0.7)	1	1	0	
Early lesion[2]	1 (0.7)	1	1	0	
Polymorphic PTLD	8 (5.9)	8	8 (100)	0	9
Monomorphic PTLD					
B-cell lymphoma	85 (63)	76	43 (57)	33 (43)	100
Aggressive B-cell lymphoma	82 (61)	75	43 (57)	32 (43)	96
Diffuse large B-cell lymphoma	54 (40)	54	31 (57)	23 (43)	64
Germinal centre type	11/50 (22)	11	1 (9)	10 (91)	
Non-germinal centre type	39/50 (78)	39	27 (69)	12 (31)	
Burkitt lymphoma/Burkitt cell leukaemia	6 (4.4)	6	4 (67)	2 (33)	7
Aggressive B-cell lymphoma, unclassifiable[3]	22 (16)	15	8 (53)	7 (47)	
B-cell lymphoma, unclassifiable[4]	3 (2.2)	1	0	1	
T/NK-cell lymphoma	17 (13)	17	2 (12)	15 (88)	20
Anaplastic large cell lymphoma, ALK-negative	5 (3.7)	5	1 (20)	4 (80)	
Peripheral T-cell lymphoma, unspecified	4 (3.0)	4	0	4 (100)	
Enteropathy-associated T-cell lymphoma	2 (1.5)	2	1	1	
Hepatosplenic T-cell lymphoma	1 (0.7)	1	0	1	
Primary cutaneous CD30 + T-cell lymphoproliferative disorder	1 (0.7)	1	0	1	
T lymphoblastic lymphoma	1 (0.7)	1	0	1	
Aggressive T-cell lymphoma, unclassifiable	3 (2.2)	3	0	3	
Classical Hodgkin lymphoma	5 (3.7)	3	3 (100)	0	6
Classical HL, nodular sclerosis	1 (0.7)	1	1	0	
Classical HL, mixed cellularity[5]	2 (1.5)	1	1	0	
HL, unspecified	2 (1.5)	1	1	0	
Unspecified lymphoma	8 (5.9)	4	3	1	
Aggressive malignant lymphoma, unclassifiable[6]	5 (3.7)	3	2	1	
Malignant lymphoma, unclassifiable[7]	3 (2.2)	1	1	0	
Indolent B-cell lymphoma	10 (7.4)	9	1 (11)	8 (89)	12
Follicular lymphoma grade 1–3a	3 (2.2)	3	0	3	
CLL/Small lymphocytic lymphoma	2 (1.5)	2	1	1	
Indolent B-cell lymphoma, unclassifiable[8]	5 (3.7)	4	0	4	

[1]Progressed to Burkitt lymphoma/Burkitt cell leukaemia; [2]Not reclassified because of missing material; [3]Five of 22 were not reclassified; [4]Two of three were not reclassified; [5]One of two was not reclassified; [6]One of five was not reclassified; [7]Two of three were not reclassified; [8]One of five was not reclassified. ALK, anaplastic lymphoma kinase; CLL, chronic lymphocytic leukaemia; EBER, EBV-encoded RNA; EBV, Epstein-Barr virus; HL, Hodgkin lymphoma; LMP-1, latent membrane protein-1; NK-cell, natural killer cell; PTLD, post-transplant lymphoproliferative disorder; PY, person-years; WHO, World Health Organization.

age in adults, median 51 versus 56 years ($p = 0.005$, Table III). The only differences regarding localisation were that EBV-positive lymphomas more frequently involved the allograft, 26% versus 9% ($p = 0.01$), and more rarely the blood or bone marrow, 5% versus 32% ($p < 0.001$). Heart, liver and lung recipients were more likely to develop an EBV-positive lymphoma ($p < 0.001$). Anti-T-cell globulin (ATG) treatment was associated with EBV-positive lymphomas, 57% versus 24% ($p < 0.001$), but not with age. No other immunosuppressive drug was correlated to EBV-status in this cohort.

EBV serology, PCR in plasma and infection

EBV serology pre-transplant was negative in 29% (23/78) of the tested recipients. EBV-seronegative recipients pre-transplant more often developed an EBV-positive lymphoma compared with seropositive recipients, 90% (18/20) versus 61% (30/49) ($p = 0.02$, Table III). The EBV-positive lymphomas occurred earlier post-transplant in EBV-seronegative compared with seropositive recipients ($p = 0.03$). EBV DNAemia at lymphoma diagnosis was detected by polymerase chain reaction (PCR) in 69% (44/64) of the tested patients and was more common in patients with EBV-positive than EBV-negative lymphomas, 92% (36/39) versus 29% (6/21) ($p < 0.001$). In the subgroup ($n = 17$) that was analysed with quantitative PCR, median EBV DNA load was 13 000 copies/ml plasma (range 100–475 000).

A symptomatic primary EBV infection with tonsillitis ($n = 5$) or fever ($n = 7$) developed in 52% (12/23) of the seronegative recipients, at a median of

Table III. Clinical characteristics of 135 patients with lymphoma/PTLD after solid organ transplantation and differences based on EBV-status.

Characteristics	All n (%) or median years (range)	Available EBV data n	n (%) or median years (range) EBV+ lymphomas	n (%) or median years (range) EBV− lymphomas	p
Sex					
Female	54 (40)	51	28 (45)	23 (40)	0.60[1]
Male	81 (60)	68	34 (55)	34 (60)	
Age at lymphoma (n = 135)	54 (0.9–79)	119	48 (0.9–76)	56 (7–79)	0.001[2]
Adults only (n = 125)	54 (20–79)	109	51 (20–76)	56 (26–79)	0.005[2]
Children only (n = 10)	14 (0.9–40)	10	16 (0.9–40)	9 (7–12)	0.70[2]
Transplanted organ					
Kidney +/− pancreas recipients	76 (56)	68	23 (37)	45 (79)	< 0.001[1]
Heart, liver, lung recipients	59 (44)	51	39 (63)	12 (21)	
Time to lymphoma (n = 135)	4.3 (0.1–26)	119	2.1 (0.1–24)	6.7 (0.2–20)	< 0.001[2]
Kidney +/− pancreas recipients (n = 76)	7.0 (0.4–26)	68	4.1 (0.5–24)	8.7 (0.4–20)	0.09[2]
Heart, liver, lung recipients (n = 59)	2.0 (0.1–12)	51	1.7 (0.1–12)	4.0 (0.2–12)	0.12[2]
Time to lymphoma subtype					
Aggressive B-cell lymphoma (n = 82)	4.0 (0.2–26)	76	2.0 (0.2–24)	7.5 (0.4–19)	< 0.001[2]
Indolent B-cell lymphoma (n = 10)	5.0 (0.7–13)	9	5.4	6.6 (1.3–13)	–
T-cell lymphoma (n = 17)	5.6 (0.2–20)	17	5.0 (3.3–6.6)	5.6 (0.2–20)	0.60[2]
Hodgkin lymphoma (n = 5)	9.5 (2.1–15)	3	9.5 (2.1–15)	–	–
Polymorphic PTLD + early lesions (n = 10)	1.5 (0.5–12)	10	1.5 (0.5–12)	–	–
Early/late lymphoma					
< 1 year post-transplant	38 (28)	32	24 (39)	8 (14)	0.002[1]
> 1 year post-transplant	97 (72)	87	38 (61)	49 (86)	
> 10 years post-transplant	29 (21)	25	8 (13)	17 (30)	0.02[1]
Localisation of lymphoma					
Only nodal disease	28 (21)	25	16 (26)	9 (16)	0.18[1]
Extranodal disease	107 (79)	94	46 (74)	48 (84)	
Allograft[3]	25 (19)	21	16 (26)	5 (9)	0.01[1]
CNS	11 (8)	9	5 (8)	4 (7)	0.55[4]
Bone marrow/blood	23 (17)	21	3 (5)	18 (32)	< 0.001[4]
Liver	17 (13)	16	9 (15)	7 (12)	0.70[1]
Lung/pleura	12 (9)	8	5 (8)	3 (5)	0.32[4]
GI tract	31 (23)	29	12 (19)	17 (30)	0.18[1]
Presentation stage (Ann Arbor) [5]					
Stage I–III	69 (54)	62	37 (63)	25 (46)	0.08[1]
Stage IV	59 (46)	51	22 (37)	29 (54)	
Performance status (ECOG) [5]					
0–1	91 (71)	82	39 (66)	43 (80)	0.11[1]
2–4	37 (29)	31	20 (34)	11 (20)	
B symptoms[5]					
Yes	62 (51)	53	29 (54)	24 (45)	0.38[1]
No	60 (49)	54	25 (46)	29 (55)	
Serum LDH[5]					
Normal	31 (33)	27	17 (39)	10 (25)	0.18[1]
Elevated	63 (67)	57	27 (61)	30 (75)	
aaIPI[5]					
0–1 point	63 (55)	56	31 (56)	25 (53)	0.75 [1]
2–3 points	52 (45)	46	24 (44)	22 (47)	
Autoimmune disease[6]	23 (17)	21	8 (13)	13 (23)	0.16[1]
Infections					
EBV seronegativity pre-SOT	23/78 (29)	20	18 (38)	2 (10)	0.02[4]
EBV, primary infection/seroconversion	21 (16)	19	18 (30)	1 (2)	< 0.001[4]
EBV DNA in blood/plasma, positive	44/64 (69)	42	36 (92)	6 (29)	< 0.001[4]
Hepatitis C	9 (7)	8	1 (1.6)	7 (12)	0.02[4]
Invasive fungal infection	15 (11)	13	9 (15)	4 (7.1)	0.16[4]
Varicella zoster infection < 1 year post-SOT	11 (8)	9	5 (8.2)	4 (7.2)	0.57[4]

[1]p-value by χ^2-test; [2]p-value by Mann-Whitney U-test; [3]When the site is the allograft, it is only registered as allograft and not as separate organ in this table; [4]p-value by Fisher's exact test; [5]Diagnosis at autopsy excluded from presentation of stage, performance status, B symptoms, LDH and aaIPI; [6]Diabetes mellitus type 1 n = 9, SLE n = 3, ulcerative colitis n = 3, in one case in combination with celiac disease, Crohn's disease n = 3, Sjögren's syndrome n = 2, one of them in combination with Crohn's disease, Juvenile arthritis n = 1, rheumatoid arthritis n = 1, autoimmune hepatitis n = 1, thyroiditis n = 1. aaIPI, age-adjusted international prognostic index; CNS, central nervous system; EBV, Epstein-Barr virus; ECOG, Eastern Cooperative Oncology Group; GI, gastrointestinal; LDH, lactate dehydrogenase; PTLD, post-transplant lymphoproliferative disorder; SOT, solid organ transplantation.

94 days (range 31–1118) post-transplant, followed by an EBV-positive lymphoma median 47 days (range 0–158) later (in one case missing EBV-status of lymphoma). Seven of the seronegative recipients developed EBV-positive lymphomas without a proven preceding symptomatic infection, whereas two had EBV-negative lymphomas and two had missing EBV-status of their lymphoma.

Association with hepatitis C

Five kidney and four liver recipients (7%) were seropositive for hepatitis C (HCV), and in seven cases a chronic infection was confirmed by PCR. The proportion of liver recipients was higher among HCV patients (4/9 vs. 15/126, $p = 0.02$), which can be explained by HCV being the indication for liver transplantation. HCV patients more often developed EBV-negative lymphomas (7/8 vs. 50/111, $p = 0.02$, Table III), their lymphomas occurred later post-transplant ($p = 0.04$), and were not localised to the graft. There was no age difference between patients with and without HCV.

Differences in DLBCL cell of origin subtype

Of the 50 DLBCL with known cell of origin, 39 (78%) were non-GC and 11 (22%) were GC ($p < 0.001$, Table II). Non-GC subtype was associated with EBV-positivity, 69% (27/39) versus 9% (1/11) ($p < 0.001$), and early occurrence, median 2.1 versus 9.8 years ($p = 0.03$). Recipients of liver, heart, lung, or pancreas compared with kidney alone were more likely to develop a non-GC subtype, 92% (23/25) versus 64% (16/25) ($p = 0.02$). Patients with non-GC-subtype were more often treated with ATG and tacrolimus than patients with GC subtype; 53% (20/38) versus 0% (0/11) ($p = 0.001$) and 33% (13/39) versus 0% (0/11) ($p = 0.02$), respectively. GC subtype was more often localised to the skeleton, 27% (3/11) versus 3% (1/39) ($p = 0.03$), but apart from this, the subtypes did not differ in localisation, age, stage, or aaIPI.

Survival analysis

At end of follow-up 25 October 2012, 27 patients were alive. Median overall survival (OS) of the 128 patients diagnosed before death was 1.4 years, and five-year OS was 39%. When excluding the 13 patients who received no treatment, most often because of rapidly progressing disease, median OS was 1.9 years, and five-year OS was 42% (Figure 1A). In order to facilitate comparison with other studies, patients that had not received treatment were excluded from further survival analysis.

EBV-positive lymphomas had better median OS compared with EBV-negative lymphomas, 5.3 versus 0.8 years ($p = 0.009$, Figure 1B). Children and young adults had better median OS compared with older patients ($p < 0.001$, Figure 1C). Half of the patients in the age spans 0–17, 18–30, and 31–45 years died, whereas 88–95% died in the age spans 46–55, 56–65, and 66–80 years. There was no difference in OS between DLBCL cell of origin subtypes (Figure 1D).

Age, type of transplant, EBV-status of lymphoma, B symptoms, performance status, extranodal disease, bone marrow/blood involvement, T-cell lymphoma, and HCV infection were associated with survival in univariate analysis and were selected for multivariate analysis (Table IV, Figure 1). Age > 45 years (or age as a continuous variable, data not shown), recipients of kidney, pancreas or heart, presence of B symptoms, ECOG 2-4, T-cell phenotype, and HCV were independent factors for inferior OS in treated patients. Extranodal disease tended to be independently associated with inferior OS ($p = 0.05$).

The most common cause of death among treated patients was lymphoma or complications to its treatment ($n = 54$, 61%), followed by other complications related to transplantation ($n = 6$, 7%), other malignancies ($n = 5$, 6%), infections not related to lymphoma treatment ($n = 4$, 5%), other causes ($n = 13$, 15%), and missing data ($n = 6$, 7%).

Treatment of lymphoma/PTLD and graft failure

Treatment of lymphoma/PTLD was very heterogeneous and is summarised in Table V. Overall, 62% achieved complete remission on initial therapy ($n = 61$) or secondary treatment ($n = 8$). The relapse rate was 23%. EBV-positive lymphomas were more likely to achieve complete remission ($p = 0.03$).

Surgery and radiation, used in localised disease, had higher response rates than chemotherapy and rituximab, but were also associated with more graft failure. Overall survival was better in those who received antiviral therapy and there was a trend in the same direction also for those who were treated with reduction of immunosuppression alone, whereas chemotherapy tended to be associated with worse outcome (Table V). The composition of cases differed substantially between treatment groups and we cannot draw far-reaching conclusions about the relative merit of these therapies.

Discussion

In this population-based study of post-transplant lymphomas covering almost three decades, we found

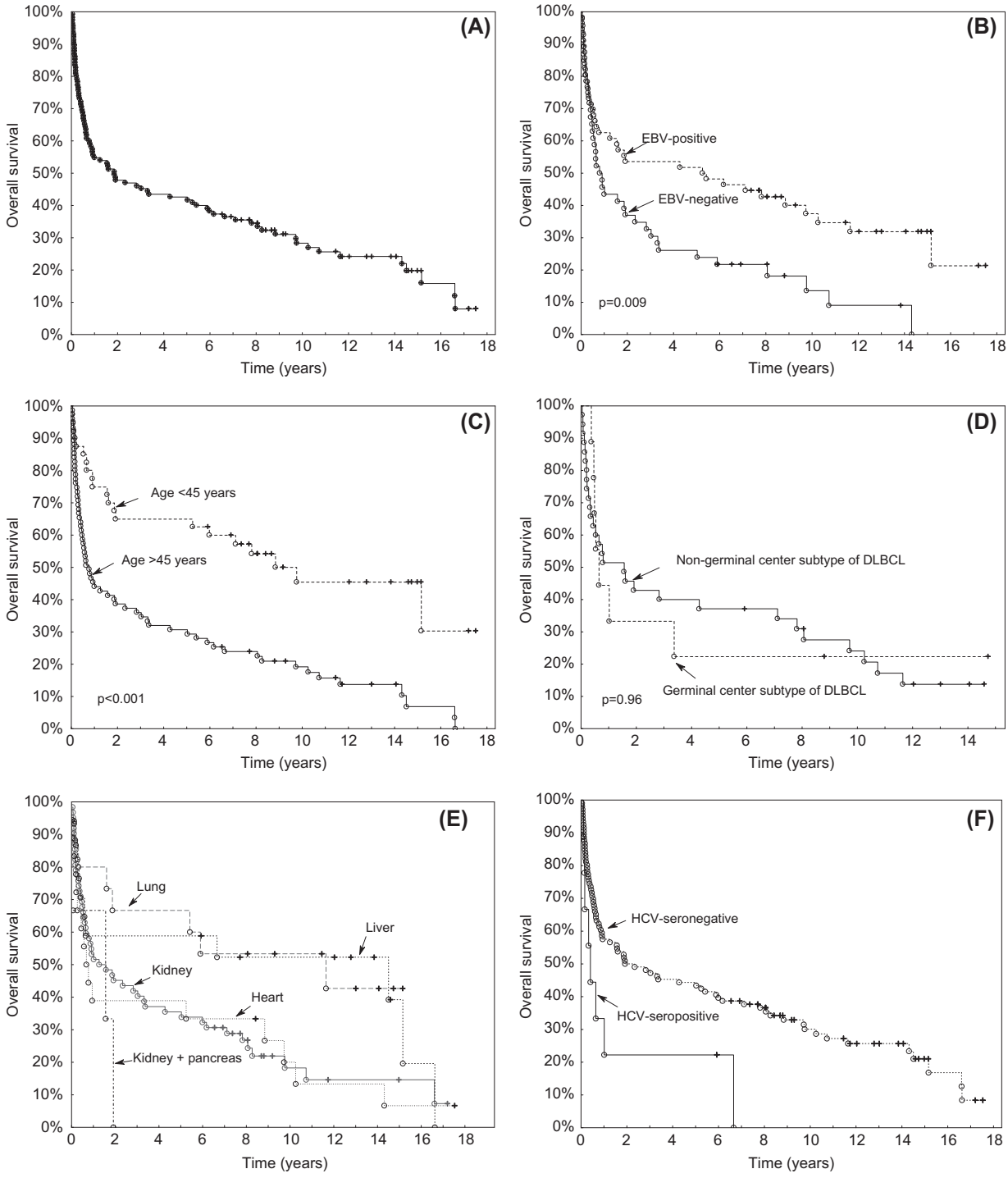

Figure 1. Overall survival in patients treated for lymphoma/PTLD after solid organ transplantation; all treated patients (A), EBV-positive versus -negative cases (B), patients aged <versus> 45 years (C), comparison between DLBCL cell of origin subtypes (D), comparison between type of organ transplant (E), and HCV-seropositive versus–seronegative recipients (F).

interesting new associations between EBV-status of lymphoma, HCV infection, lymphoma subtype, and clinical data. The incidence rate is somewhat lower than in two recent large US studies, 159 versus 194 and 204 per 100 000 person-years, respectively, especially since polymorphic PTLD were not included in the two studies [2,3]. Organ-specific incidence was not calculated in this study, but we have previously reported in almost the same cohort (Swedish SOT recipients between 1970 and 2008), however without re-evaluation of the lymphomas, a lower incidence rate of non-Hodgkin lymphomas (NHL) in kidney recipients and higher in liver, heart and lung recipients compared with Engels et al.

Table IV. Analysis of prognostic factors for overall survival in 115 patients treated for lymphoma/PTLD after solid organ transplantation.

			Univariate analysis[1]		Multivariate analysis[1]	
Prognostic factor	n	n (%) of deaths	Hazards ratio (95% CI)	p	Hazards ratio (95% CI)	p
Age at lymphoma	115	88 (77)	1.02 (1.01–1.04)	0.001		
Age > 45 years	75	67 (89)	1.0 (ref)			
Age < 45 years	40	21 (53)	0.37 (0.23–0.61)	< 0.001	0.19 (0.10–0.36)	< 0.001
Male	70	52 (74)	1.0 (ref)			
Female	45	36 (80)	1.27 (0.83–1.94)	0.28		
Kidney/pancreas/heart recipients	83	69 (83)	1.0 (ref)			
Liver/lung recipients	32	19 (59)	0.49 (0.29–0.82)	0.006	0.45 (0.24–0.86)	0.02
EBV-positive lymphoma	56	37 (66)	1.0 (ref)			
EBV-negative lymphoma	46	40 (87)	1.88 (1.19–2.98)	0.007	1.03 (0.54–1.96)	0.94
B symptoms, no	56	38 (68)	1.0 (ref)			
B symptoms, yes	54	45 (83)	1.96 (1.27–3.04)	0.002	2.59 (1.38–4.84)	0.003
Elevated serum LDH	55	45 (82)	1.0 (ref)			
Normal serum LDH	29	17 (59)	0.58 (0.33–1.01)	0.05		
Performance status, ECOG 0–1	83	62 (75)	1.0 (ref)			
Performance status, ECOG 2–4	32	26 (81)	1.74 (1.09–2.77)	0.02	2.05 (1.04–4.01)	0.04
Stage I–III	67	47 (70)	1.0 (ref)			
Stage IV	48	41 (85)	1.48 (0.97–2.26)	0.07		
aaIPI 0–1 point	59	41 (69)	1.0 (ref)			
aaIPI 2–3 points	44	36 (82)	1.37 (0.87–2.16)	0.17		
Extranodal disease	88	72 (82)	1.0 (ref)			
Nodal disease only	27	16 (59)	0.54 (0.31–0.92)	0.02	0.49 (0.24–1.00)	0.051
No allograft involvement	95	76 (80)	1.0 (ref)			
Allograft involvement	20	12 (60)	0.59 (0.32–1.09)	0.09		
Bone marrow/blood involvement, no	101	74 (73)	1.0 (ref)			
Bone marrow/blood involvement, yes	14	14 (100)	2.32 (1.30–4.17)	0.005	0.87 (0.42–1.79)	0.71
CNS involvement, no	105	79 (75)	1.0 (ref)			
CNS involvement, yes	10	9 (90)	1.84 (0.91–3.72)	0.09		
T-cell lymphoma, no	100	73 (73)	1.0 (ref)			
T-cell lymphoma, yes	15	15 (100)	3.42 (1.92–6.09)	< 0.001	3.52 (1.73–7.15)	< 0.001
Monomorphic lymphomas	105	82 (78)	1.0 (ref)			
Polymorphic PTLD + early lesions	10	6 (60)	0.63 (0.28–1.45)	0.28		
Late-onset lymphoma	83	67 (81)	1.0 (ref)			
Early-onset lymphoma	32	21 (66)	0.69 (0.42–1.13)	0.14		
ATG treatment, never	63	49 (78)	1.0 (ref)			
ATG treatment, ever	48	35 (73)	0.65 (0.42–1.03)	0.07		
Hepatitis C infection, never	106	80 (75)	1.0 (ref)			
Hepatitis C infection, ever	9	8 (89)	2.16 (1.03–4.52)	0.04	2.81 (1.12–7.08)	0.03

[1]By Cox proportional hazards regression model. aaIPI, age-adjusted International Prognostic Index; ATG, anti-T-cell globulin; CI, confidence interval; CNS, central nervous system; EBV, Epstein-Barr virus; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; PTLD, post-transplant lymphoproliferative disorder.

[2,12]. We also noticed a decline in NHL risk in the 21st century among non-kidney recipients compared with the 1990s, possibly because of a change in immunosuppressive regimens [12]. There was a higher proportion of kidney transplants in the Swedish cohort compared with the US study (74% vs. 58%) and consequently a lower proportion of liver and heart recipients [2,12]. Moreover, ATG has been more widely used in the US than in Sweden, in particular in kidney transplantations. The combination that we have a higher proportion of kidney recipients and that this group have a lower incidence rate, possibly because of a more restrictive use of ATG, may in part explain the lower incidence rate overall in this study. Furthermore, even if the Swedish National Inpatient and Cancer Register have a high coverage rate and reliability [13], we know of additional cases that have not been identified by the registers, which we did not include in order not to introduce a bias.

In terms of incidence rate by lymphoma subtype, we report a higher incidence of T-cell lymphomas (20 vs. 10 per 100 000 person-years), a somewhat lower incidence of Hodgkin lymphoma (6 vs. 10) and Burkitt lymphoma (7 vs. 11), and a much lower incidence of DLBCL (64 vs. 120) compared with Clarke et al. [3]. However, when adding the cases of unclassifiable aggressive B-cell lymphomas to DLBCL, the difference is not as striking (89 vs. 120).

We report a lower proportion of early lesions and polymorphic PTLD than other large retrospective

Table V. Initial treatment of lymphoma and development of graft failure in 115 treated patients.

	All treated		CR		OS[2]	Graft failure	
Initial therapy[1]	n	%	n	%	p[3]	n	%
Initial therapy, any	115		61/111	55		27	23
Reduction in immunosuppression alone[4]	21	18	12/21	57	0.08	6	29
Rituximab, total	21	18	11/21	52	0.84[5]	3	14
Alone[6]	2	2	0/2	0		0	0
Chemotherapy, total	73	63	38/71	54	0.12	13	18
Alone[6]	34	30	12/33	36		4	12
CHOP-like[7]	59	51	32/57	56	0.65	12	20
+ rituximab	19	17	11/19	58		3	16
+ surgery	12	10	8/11	73		2	17
+ radiotherapy	11	10	8/11	73		4	36
Surgery, total	27	23	18/25	72	0.96	9[8]	33
Alone[6]	12	10	7/11	64		6	50
+ radiotherapy	3	3	3/3	100		1	33
Radiotherapy, total	18	16	12/17	71	0.40	6[9]	33
Alone[6]	4	3	1/3	33		1	25
Antiviral therapy (+ any other therapy)	34	30	18/33	55	0.01	8	24

[1]No missing data on initial therapy; [2]Comparison with all other treated patients (patients not receiving any treatment excluded from calculation); [3]p-value by log rank test; [4]Doses were approximately halved; [5]Analysed in the subgroup of B-cell phenotype; [6]With or without reduction in immunosuppression; [7]CHOP-like chemotherapy was defined as CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone), CNOP (doxorubicin replaced with mitoxantrone), CHOEP (CHOP + etoposide) or VACOP-B (doxorubicin, cyclophosphamide, vincristine, bleomycin, etoposide and prednisone); [8]In five cases the graft failure is explained by total or partial transplantectomy; [9]Only in one of the six cases with graft failure, the allograft was irradiated. CR, complete response; OS, overall survival.

studies, 7% versus approximately 30%, probably because these diagnoses are not consequently reported to the cancer register [14,15]. The proportion of T-cell lymphomas is somewhat higher than in recent large studies, 13% versus 5–7% [3,16,17]. Furthermore, there was a higher proportion of EBV-negative lymphomas, which constituted about half of the cases, which may be a consequence of the long observation period, the low proportion of polymorphic PTLD, and the high proportion of T-cell lymphomas in our study and/or under-reporting of EBV-negative cases historically [3,5]. In accordance with other retrospective studies with long follow-up, we had a high proportion of PTLDs diagnosed more than 10 years post-transplant [14,16].

Half of the EBV-seronegative recipients developed a symptomatic EBV infection followed by a lymphoma within five months. Although the benefit of routine EBV PCR monitoring in adults is uncertain, it is advisable to monitor SOT recipients with primary EBV infection weekly by EBV PCR in plasma for half a year after the infection in order to permit early PTLD diagnosis and treatment [18].

We confirm that EBV-positive lymphomas are often localised to the allograft or to organs in the vicinity of the graft, which supports that chronic antigenic stimulation by the graft may contribute to the development of malignancies after transplantation [1,6]. EBV-negative PTLDs are suggested to be caused by long-term immunosuppressive treatment, EBV through "hit and run" oncogenesis, or other chronic viral infections or to represent a coincidental lymphoma in a transplant recipient [7,19]. Hepatitis C has been proposed to play a causative role in the development of B-cell lymphomas through chronic antigenic stimulation or clonal expansion of B-cells, in immunocompetent individuals as well as transplant recipients, both liver and other organs [20,21]. We found an association between hepatitis C infection and EBV-negative lymphomas suggesting a possible role in late-onset PTLD. However, in the majority of EBV-negative PTLDs, the aetiology remains unknown.

Younger age, absence of B symptoms, and better performance status were independently associated with better survival, in accordance with previous studies [17,22–24]. Recipients of kidney, pancreas or heart were independently associated with increased risk of death compared with recipients of liver and lung (Figure 1E). This finding is in conflict with previous reports where liver recipients had a worse outcome in terms of overall survival or response to rituximab, whereas heart recipients had a better prognosis [16,25]. Hepatitis C infection was an independent poor prognostic factor, which has not been reported before to the best of our knowledge (Figure 1F). Hepatitis C has previously been associated with inferior survival in PTLD in univariate

analysis in small series of patients [26,27]. Hepatitis C has also been associated with inferior long-term patient and graft survival in kidney transplantation without PTLD. Also in our study, the number of hepatitis C patients is limited and larger studies are needed to confirm this finding. Further, T-cell phenotype was independently associated with poor survival, which has recently been reported in kidney recipients [17].

Studies on the prognostic importance of DLBCL cell of origin subtypes post-SOT in a clinical setting are small and limited [9,28]. In the largest previous study, there was no difference in survival in 27 patients with monomorphic B-cell PTLD, although there was a trend that GC subtype did worse [9]. Nor could we demonstrate any difference in survival between the subgroups, and even though the number of patients is limited, DLBCL cell of origin subtype seems to lack prognostic importance in the transplant setting.

Non-GC subtype of DLBCL post-transplant has previously been associated with EBV, and we show in a large population-based cohort post-transplant that non-GC subtype constitutes three quarters of DLBCL, is more frequently EBV-positive, and develops more often in recipients of liver, heart, lung or pancreas, unlike a previously reported association between liver recipients and GC-subtype [9,10,19]. We also found that patients with non-GC subtype were more likely to have received ATG and tacrolimus. Non-GC PTLD, albeit morphologically indistinguishable from B-cell lymphomas in the immunocompetent hosts, have been reported to represent a distinct type of lymphoma by gene expression profiling and appear closely related to activated memory B-cells – the reservoir of latent EBV infection [29]. Possibly, the heavier immunosuppression associated with non-kidney transplantations leads to uncontrolled proliferation of these cells and development of PTLD [9,28].

Median OS and five-year survival of all treated patients in this study was only 1.9 years and 42%, respectively, although in line with some studies from the last decade [15,16]. The high proportion of monomorphic PTLD, toxicity to chemotherapy, but also patients and doctors delay, may explain the poor survival. Much to our disappointment, the outcome for those treated with rituximab was not better, as opposed to some recent studies [14,25] but consistent with others [15,16]. There might have been selection bias for rituximab to more severely ill patients. Furthermore, the rituximab group was compared with a selected subgroup that responded well to reduction in immunosuppression alone. Patients that received antiviral therapy for their lymphoma had better survival, probably because of a correlation with EBV-positive cases that also had a better outcome in univariate analysis.

The limitations of our retrospective study include the difficulty to determine certain variables and the lack of a defined treatment approach. The cohort cannot be considered as population-based regarding early lesions and polymorphic PTLD. Nevertheless, we consider that this cohort of lymphomas post-SOT has unique strengths in being large and detailed regarding clinical and histological data and with long follow-up time.

In conclusion, we show that a large proportion of lymphoma occurs late, up to 26 years, after SOT and that almost half of them are EBV-negative. EBV-negative lymphomas had a different clinical presentation and were occasionally associated to hepatitis C infection. HCV infection was revealed as a new independent prognostic factor for poor survival that needs to be confirmed in larger studies. EBV-positive lymphomas had better survival but EBV-status was not independently associated to survival. Furthermore, we observed that most DLBCL were of the non-GC subtype and did not have inferior survival. DLBCL cell of origin subtype seems to lack prognostic importance in the transplant setting.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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References

[1] Opelz G, Dohler B. Lymphomas after solid organ transplantation: A collaborative transplant study report. Am J Transplant 2004;4:222–30.

[2] Engels EA, Pfeiffer RM, Fraumeni JF, Jr., Kasiske BL, Israni AK, Snyder JJ, et al. Spectrum of cancer risk among US solid organ transplant recipients. JAMA 2011;306:1891–901.

[3] Clarke CA, Morton LM, Lynch C, Pfeiffer RM, Hall EC, Gibson TM, et al. Risk of lymphoma subtypes after solid organ transplantation in the United States. Br J Cancer 2013;109:280–8.

[4] Quinlan SC, Pfeiffer RM, Morton LM, Engels EA. Risk factors for early-onset and late-onset post-transplant lymphoproliferative disorder in kidney recipients in the United States. Am J Hematol 2011;86:206–9.

[5] Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, et al., editors. WHO classification of tumors of haemotopoietic and lymphoid tissue, 4 ed. Lyon: IARC; 2008.

[6] Caillard S, Lamy FX, Quelen C, Dantal J, Lebranchu Y, Lang P, et al. Epidemiology of posttransplant lymphoproliferative disorders in adult kidney and kidney pancreas recipients: Report of the French registry and

analysis of subgroups of lymphomas. Am J Transplant 2012;12:682–93.

[7] Nelson BP, Nalesnik MA, Bahler DW, Locker J, Fung JJ, Swerdlow SH. Epstein-Barr virus-negative post-transplant lymphoproliferative disorders: A distinct entity? Am J Surg Pathol 2000;24:375–85.

[8] Caillard S, Dharnidharka V, Agodoa L, Bohen E, Abbott K. Posttransplant lymphoproliferative disorders after renal transplantation in the United States in era of modern immunosuppression. Transplantation 2005;80:1233–43.

[9] Johnson LR, Nalesnik MA, Swerdlow SH. Impact of Epstein-Barr virus in monomorphic B-cell posttransplant lymphoproliferative disorders: A histogenetic study. Am J Surg Pathol 2006;30:1604–12.

[10] Capello D, Cerri M, Muti G, Berra E, Oreste P, Deambrogi C, et al. Molecular histogenesis of posttransplantation lymphoproliferative disorders. Blood 2003;102:3775–85.

[11] Hans CP, Weisenburger DD, Greiner TC, Gascoyne RD, Delabie J, Ott G, et al. Confirmation of the molecular classification of diffuse large B-cell lymphoma by immunohistochemistry using a tissue microarray. Blood 2004;103:275–82.

[12] Fernberg P, Edgren G, Adami J, Ingvar A, Bellocco R, Tufveson G, et al. Time trends in risk and risk determinants of non-Hodgkin lymphoma in solid organ transplant recipients. Am J Transplant 2011;11:2472–82.

[13] Ludvigsson JF, Andersson E, Ekbom A, Feychting M, Kim JL, Reuterwall C, et al. External review and validation of the Swedish national inpatient register. BMC Public Health 2011;11:450.

[14] Evens AM, David KA, Helenowski I, Nelson B, Kaufman D, Kircher SM, et al. Multicenter analysis of 80 solid organ transplantation recipients with post-transplantation lymphoproliferative disease: Outcomes and prognostic factors in the modern era. J Clin Oncol 2010;28:1038–46.

[15] Ghobrial IM, Habermann TM, Maurer MJ, Geyer SM, Ristow KM, Larson TS, et al. Prognostic analysis for survival in adult solid organ transplant recipients with post-transplantation lymphoproliferative disorders. J Clin Oncol 2005;23:7574–82.

[16] Dierickx D, Tousseyn T, Sagaert X, Fieuws S, Wlodarska I, Morscio J, et al. Single-center analysis of biopsy-confirmed posttransplant lymphoproliferative disorder: Incidence, clinicopathological characteristics and prognostic factors. Leuk Lymphoma Epub 2013 Apr 9.

[17] Caillard S, Porcher R, Provot F, Dantal J, Choquet S, Durrbach A, et al. Post-transplantation lymphoproliferative disorder after kidney transplantation: Report of a nationwide French registry and the development of a new prognostic score. J Clin Oncol 2013;31:1302–9.

[18] Parker A, Bowles K, Bradley JA, Emery V, Featherstone C, Gupte G, et al. Diagnosis of post-transplant lymphoproliferative disorder in solid organ transplant recipients – BCSH and BTS Guidelines. Br J Haematol 2010;149: 675–92.

[19] Morscio J, Dierickx D, Ferreiro JF, Herreman A, Van Loo P, Bittoun E, et al. Gene expression profiling reveals clear differences between EBV-positive and EBV-negative post-transplant lymphoproliferative disorders. Am J Transplant 2013;13:1305–16.

[20] Aucejo F, Rofaiel G, Miller C. Who is at risk for post-transplant lymphoproliferative disorders (PTLD) after liver transplantation? J Hepatol 2006;44:19–23.

[21] Peveling-Oberhag J, Arcaini L, Hansmann ML, Zeuzem S. Hepatitis C-associated B-cell non-Hodgkin lymphomas. Epidemiology, molecular signature and clinical management. J Hepatol 2013;59:169–77.

[22] Choquet S, Oertel S, LeBlond V, Riess H, Varoqueaux N, Dorken B, et al. Rituximab in the management of post-transplantation lymphoproliferative disorder after solid organ transplantation: Proceed with caution. Ann Hematol 2007; 86:599–607.

[23] Tsai DE, Hardy CL, Tomaszewski JE, Kotloff RM, Oltoff KM, Somer BG, et al. Reduction in immunosuppression as initial therapy for posttransplant lymphoproliferative disorder: Analysis of prognostic variables and long-term follow-up of 42 adult patients. Transplantation 2001;71: 1076–88.

[24] Leblond V, Dhedin N, Mamzer Bruneel MF, Choquet S, Hermine O, Porcher R, et al. Identification of prognostic factors in 61 patients with posttransplantation lymphoproliferative disorders. J Clin Oncol 2001;19:772–8.

[25] Trappe R, Oertel S, Leblond V, Mollee P, Sender M, Reinke P, et al. Sequential treatment with rituximab followed by CHOP chemotherapy in adult B-cell post-transplant lymphoproliferative disorder (PTLD): The prospective international multicentre phase 2 PTLD-1 trial. Lancet Oncol 2012;13:196–206.

[26] Caillard S, Lelong C, Pessione F, Moulin B. Post-transplant lymphoproliferative disorders occurring after renal transplantation in adults: Report of 230 cases from the French Registry. Am J Transplant 2006;6:2735–42.

[27] Reshef R, Vardhanabhuti S, Luskin MR, Heitjan DF, Hadjiliadis D, Goral S, et al. Reduction of immunosuppression as initial therapy for posttransplantation lymphoproliferative disorder (bigstar). Am J Transplant 2011; 11:336–47.

[28] Lucioni M, Capello D, Riboni R, Ippoliti G, Campana C, Bandiera L, et al. B-cell posttransplant lymphoproliferative disorders in heart and/or lungs recipients: Clinical and molecular-histogenetic study of 17 cases from a single institution. Transplantation 2006;82:1013–23.

[29] Vakiani E, Basso K, Klein U, Mansukhani MM, Narayan G, Smith PM, et al. Genetic and phenotypic analysis of B-cell post-transplant lymphoproliferative disorders provides insights into disease biology. Hematol Oncol 2008;26:199–211.