ACTA ONCOLOGICA
2021, VOL. 60, NO. 6, 771–778
https://doi.org/10.1080/0284186X.2021.1904520

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ORIGINAL ARTICLE

Prior antithymocyte globulin therapy and survival in post-transplant lymphoproliferative disorders

Amelie Kinch[a], Eva Baecklund[b], Daniel Molin[c], Karlis Pauksens[a], Christer Sundström[d], Gunnar Tufveson[e] and Gunilla Enblad[c]

[a]Department of Medical Sciences, Section of Infectious Diseases, Uppsala University, Uppsala, Sweden; [b]Department of Medical Sciences, Section of Rheumatology, Uppsala University, Uppsala, Sweden; [c]Experimental and Clinical Oncology, Department of Immunology, Genetics and Pathology, Uppsala University, Uppsala, Sweden; [d]Department of Immunology, Genetics and Pathology, Uppsala University, Uppsala, Sweden; [e]Department of Surgical Sciences, Uppsala University, Uppsala, Sweden

ABSTRACT

Background: Treatment with antithymocyte globulin (ATG) is a well-recognized risk factor for the development of post-transplant lymphoproliferative disorders (PTLD) after solid organ transplantation, but it is unknown how its use affects overall survival after PTLD.

Methods: A total of 114 patients with PTLD and available data on immunosuppressive regimen were included from a nation-wide case series of solid organ transplant recipients in Sweden. Prior use of ATG was correlated to clinical features, PTLD subtype, and survival.

Results: A total of 47 (41%) patients had received ATG prior to the diagnosis of PTLD. The ATG-treated patients were more likely to be recipients of hearts or lungs, and less likely of kidneys ($p < 0.01$). They had experienced more acute rejections ($p = 0.02$). The PTLDs arose earlier, median 2.0 vs. 6.6 years post-transplant ($p = 0.002$) and were more often situated in the allograft (32% vs. 7%, $p < 0.001$) in patients with prior ATG vs. no ATG treatment. The PTLDs in the ATG group were more often Epstein–Barr virus-positive (80% vs. 40%, $p < 0.001$). There were more polymorphic PTLDs (17% vs. 1.5%, $p = 0.004$) and less T-cell PTLDs (4% vs. 19%, $p = 0.02$) in the ATG group than in the no ATG group. Diffuse large B-cell lymphoma was equally common in patients with and without prior ATG therapy, but the non-germinal center subtype was more frequent in the ATG group ($p = 0.001$). In an adjusted Cox proportional hazards regression model, prior ATG treatment and better performance status were associated with superior overall survival, whereas older age, T-cell subtype of PTLD, presence of B symptoms, and elevated lactate dehydrogenase were associated with inferior overall survival. Patients receiving ATG solely as rejection therapy had superior overall survival compared with those receiving ATG as induction therapy or both ($p = 0.03$).

Conclusions: ATG therapy, especially rejection therapy, prior to PTLD development is an independent prognostic factor for superior overall survival after PTLD diagnosis.

ARTICLE HISTORY
Received 15 January 2021
Accepted 12 March 2021

KEYWORDS
PTLD; ATG; solid organ transplantation; prognosis

Introduction

Post-transplant lymphoproliferative disorder (PTLD) is a complication to solid organ transplantation with high mortality rates. The diagnosis comprises nondestructive PTLD (previously called early lesions), polymorphic PTLD, monomorphic B- and T-cell PTLD, and classical Hodgkin lymphoma-like PTLD [1]. Epstein–Barr virus (EBV) plays a role in the pathogenesis and can be detected in the tumor in almost all cases of nondestructive PTLD, more than 90% of cases of polymorphic and Hodgkin lymphoma-like PTLD, and approximately 50% of monomorphic PTLD [1–3].

Transplantation of an organ from an EBV-seropositive donor to an EBV-seronegative recipient is a well-established risk factor for EBV-related PTLD [4]. EBV-positive (EBV+) PTLD is associated with early-onset, that is, development within one year post-transplant. Risk for PTLD is further associated with the immunosuppressive therapy but the contribution of each immunosuppressive agent is not clear. Use of T-cell depleting antibodies, such as antithymocyte globulin (ATG) and muromonab-CD3 (OKT-3), has been associated with the development of early-onset PTLD in particular, whereas long-term use of calcineurin inhibitors (cyclosporine and tacrolimus) has been associated with late-onset PTLD [5–10]. High rates of EBV + PTLD have been reported when belatacept was used at high dosage in EBV-seronegative kidney transplant recipients [11]. In addition to EBV and immunosuppression, the type of solid organ transplant is an important risk factor for PTLD with the highest incidence found in intestinal recipients, followed by a declining incidence in lung, heart, liver, and pancreatic recipients, and the lowest incidence found in kidney recipients [1,12].

CONTACT Amelie Kinch amelie.kinch@medsci.uu.se Department of Medical Sciences, Section of Infectious Diseases, Uppsala University, Uppsala, S-751 85, Sweden

Survival in PTLD has improved in recent years due to an increased awareness of the diagnosis, the introduction of rituximab as PTLD treatment, and sequential treatment with rituximab followed by chemotherapy [13]. Older age, poor performance status, the presence of B symptoms (fever, night sweats, and weight loss), elevated serum lactate dehydrogenase (S-LDH), advanced stage, higher International Prognostic Index (IPI) score, extranodal disease, central nervous system (CNS) involvement, bone marrow involvement, monomorphic PTLD (and especially T-cell phenotype), hypoalbuminemia, elevated serum creatinine level (for kidney transplantation), type of transplant (thoracic organ), and hepatitis C infection have been reported as independent prognostic factors for inferior survival in various case series [2,5,14–20]. Immunosuppressive regimens have seldom been included in these analyses of prognostic factors. Prior therapy with muromonab-CD3 has been associated with inferior survival in one study of kidney recipients but the result was not confirmed in a larger cohort [4,5]. ATG has not been reported as a prognostic factor to the best of our knowledge.

ATG consists of polyclonal IgG antibodies derived from rabbits (e.g. Thymoglobulin and ATG Fresenius) or horses (e.g. Lymphoglobulin and Atgam) that were immunized with thymocytes or T-cell lines [21]. The different ATG preparations differ in terms of potency and efficacy but share common properties such as causing profound depletion of T-cells and other leukocytes through complement-dependent and cell-mediated cytotoxicity or *via* apoptosis induction. ATG has been commonly used for induction therapy to prevent acute allograft rejection as well as for treatment of acute rejection in solid organ transplantation. PTLD is a feared complication of ATG use, but it is unknown if prior use of ATG affects overall survival after the diagnosis of PTLD in solid organ transplantation. Therefore, we studied the correlations between prior ATG use and clinical features, PTLD subtype, and overall survival in 114 solid organ recipients diagnosed with PTLD in a nationwide case series with long follow-up time.

Materials and methods

Patients

The PTLD cases were retrieved from a previously reported population-based case series of lymphoproliferative disorders after solid organ transplantation between 1980 and 2006 in Sweden [2]. In the Swedish National Inpatient Register, 10,010 solid organ transplant recipients between 1970 and 2006 were identified. These individuals were then linked to the information in the Swedish Cancer Register through the Swedish personal identity number, thereby identifying all recipients who developed lymphoproliferative disorders post-transplant between 1980 and 2006 in Sweden. Only two cases of PTLD were reported between 1970 and 1980 and these cases were not included. Reporting of newly diagnosed cancers to the Cancer Register is mandatory for clinicians and pathologists in Sweden resulting in an excellent completeness of the register [22]. However, nondestructive and polymorphic PTLD are not consequently reported. After extraction of data from the medical records and reevaluation of the tumor biopsies, there were 125 confirmed cases of PTLD. Since this study focused on ATG and survival, all cases with missing data on ATG treatment ($n = 4$) and all PTLDs diagnosed at autopsy ($n = 7$) were excluded. The final study population thus included 114 solid organ transplant recipients who had developed PTLD and had available information on ATG treatment.

Clinical data were obtained by one physician (AK) from the medical records at the transplantation centers and from the hospitals where the medical follow-up was performed. All patients were followed from the date of the transplantation until death or end of follow-up (25 October 2012), which-ever occurred first. The study was approved by the Regional Ethical Review Board in Uppsala, Sweden (No 2007/150).

Reevaluation of PTLDs

The tumor biopsies have been reevaluated according to the 2008 revision of the WHO classification of lymphoid neoplasms by an experienced hematopathologist (CS) and the diagnoses are consistent with the latest revision of 2016 [1]. Cell-of-origin classification of diffuse large B-cell lymphoma (DLBCL) into germinal center or nongerminal center subtype was based on immunohistochemistry and the Hans algorithm [23]. EBV-status of PTLD was analyzed by EBV-encoded RNA (EBER) *in situ* hybridization.

Statistics

Chi-square or Fisher's exact test (if <5 observations) was used for categorical variables and Mann-Whitney U-test for continuous variables with two-sided *p*-values. Overall survival was calculated from the time of PTLD diagnosis to death from any cause by Kaplan–Meier time-to-event analysis. PTLD-specific survival was measured from PTLD diagnosis to death from PTLD. Differences in survival were evaluated using log-rank test. Prognostic factors for overall survival in PTLD was analyzed by the Cox proportional hazards regression model. We adjusted for age linearly. We tested the proportional hazards assumption, which was not violated. *P*-values <0.05 was considered statistically significant. Statistica Software (TIBCO Software Inc.) was used in all analyses.

Results

Use of ATG and clinical features

Forty-seven (41%) of the 114 solid organ transplant recipients in our case series had received ATG (ATG group) and 67 (59%) had not received ATG (no ATG group) prior to the diagnosis of PTLD. ATG was given as induction therapy ($n = 28$), rejection therapy ($n = 13$), or both ($n = 6$). The ATG-treated patients received a median of five (range 2–15) doses of ATG. At least three different formulations of rabbit ATG and two formulations of horse ATG were used. Since these

ATG preparations have different recommended dosages to prevent organ rejection, comparisons of ATG doses were not feasible.

The patients in the ATG group were median 50 years old at the time of PTLD diagnosis, which was not significantly younger than the age of 54 years in the no ATG group (Table 1). Heart and lung transplant recipients were overrepresented in the ATG group, whereas there was a predominance of kidney transplant recipients in the no ATG group ($p < 0.01$ for all). The ATG-treated patients had experienced more episodes of acute rejections than the patients in the no ATG group ($p = 0.02$). However, incidence of graft failure, retransplantation, or type of immunosuppressive regimens besides ATG did not differ between the two groups.

EBV serology before transplantation was known in 59% of the patients; 67% were EBV seropositive and 33% were seronegative. EBV serostatus pretransplant did not differ between the ATG and the no ATG group ($p = 0.66$).

The PTLDs occurred earlier post-transplant, median 2.0 vs. 6.6 years after the latest transplantation, in patients with prior ATG treatment than in those without ($p = 0.002$). The PTLDs arose median 1.5 years (range, 0.04-17 years) after last ATG exposure. Polymorphic and B-cell monomorphic PTLD tended to develop earlier after last ATG dose compared with T-cell PTLD, but the difference was not statistically significant ($p = 0.14$).

The most common localization of PTLD in the ATG group was in the allograft and engagement of the allograft was more frequent in the ATG group compared with the no ATG group (32% vs. 7%, $p < 0.001$). Besides the predilection to the allograft, the PTLDs were similarly located in the patients who had or had not received ATG. Presentation stage, performance status according to the Eastern Cooperative Oncology Group (ECOG), presence of B symptoms, S-LDH level, and age-adjusted IPI were similar in the two groups.

ATG and PTLD subtype

The PTLDs that developed after ATG treatment were more frequently polymorphic or nondestructive PTLD (17% vs. 1.5%, $p = 0.004$) and more rarely monomorphic T-cell (4% vs. 19%, $p = 0.02$) compared with the distribution of PTLD subtypes in the no ATG group (Table 1). The frequency of DLBCL did not differ between the groups (approximately 45% in both groups), but the non-germinal center subtype was more common among ATG-treated than nontreated patients with DLBCL PTLD (100% vs. 61%, $p = 0.001$). The PTLDs occurring in the ATG group were more often EBV + in tumor tissue than the PTLDs in the no ATG group (80% vs. 40%, $p < 0.001$).

ATG and outcome

Complete response on first or secondary treatment of PTLD was achieved in 73% of the patients in the ATG group and 56% in the no ATG group ($p = 0.09$). The treatment of PTLD was heterogeneous but did not differ significantly between the groups (Table 1). However, there was a trend that reduction of immunosuppression as single PTLD treatment was more common in the ATG group compared with the no ATG group (19% vs. 9%, $p = 0.11$). Patients with reduction of immunosuppression as sole PTLD treatment tended to have a superior overall survival ($p = 0.052$) whereas none of the other PTLD regimens (chemotherapy, rituximab, radiation, surgery) proved to be superior when compared with all other treatments. We assume there was a selection bias for rituximab and chemotherapy to more severely ill patients.

In total, median overall survival was 1.0 year and five-year overall survival was 40% from the diagnosis of PTLD. Median PTLD-specific survival was 6.7 years and PTLD-specific five-year survival was 51%. In the ATG group, median overall survival was 5.4 years, five-year overall survival was 51%, median PTLD-specific survival was not reached, and PTLD-specific five-year survival was 63% (Figure 1). In the no ATG group, median overall survival was 0.7 years, five-year overall survival was 32%, median PTLD-specific survival was 0.6 years, and PTLD-specific five-year survival was 43%.

The patients who developed PTLD after ATG treatment both had superior overall survival ($p = 0.02$) and PTLD-specific survival ($p = 0.03$) compared with the patients with PTLD without prior ATG therapy (Figure 1(A,B)). Also in the subgroup of 52 DLBCLs, patients with prior ATG tended to have superior overall survival ($p = 0.17$), but sample size was probably not large enough to prove a difference.

There was no dose-response relationship between number of ATG doses and survival. The difference in overall survival was mainly explained by a better survival in the patients who received ATG solely as rejection therapy as compared with ATG as induction therapy or both ($p = 0.03$, Figure 1(C)).

In the ATG group, 34 of 47 patients had died at end of follow-up and PTLD was the cause of death in 18 cases. In the no ATG-group, 54 of 67 patients died and PTLD was the cause of death in 39 cases.

Age at PTLD diagnosis, type of transplant (lung vs. other organ), T-cell subtype of PTLD, presence of B symptoms, performance status, S-LDH, and prior ATG treatment were associated with overall survival in unadjusted Cox proportional hazards regression analysis and were selected together with stage for multivariable analysis (Table 2). In adjusted Cox proportional hazards regression analysis, prior ATG treatment and better performance status were associated with superior overall survival whereas older age, T-cell subtype of PTLD, the presence of B symptoms, and elevated S-LDH were associated with inferior overall survival.

Discussion

In this nationwide case series of 114 solid organ transplant recipients with PTLD, we found that ATG treatment prior to the diagnosis of PTLD was an independent prognostic factor for superior overall survival. Well-recognized markers of disease burden and prognosis such as age, stage, performance status, the presence of B symptoms, LDH level, and age-adjusted IPI were comparable between the patients who had versus had not received ATG. However, there were more recipients of hearts and lungs and more episodes of acute rejections in the ATG group.

Table 1. Clinical characteristics of and distribution of PTLD subtypes in solid organ recipients who did versus did not receive ATG prior to development of PTLD.

		N (%) or median (range, min-max)		
	All	ATG	No ATG	*p* Value
N	114	47 (41)	67 (59)	
Age at PTLD diagnosis, years	52.6 (0.9–75.6)	49.8 (16.4–75.2)	54.0 (0.9–75.6)	0.25
Sex				
Male	69 (61)	28 (60)	41 (61)	0.86
Female	45 (39)	19 (40)	26 (39)	
Type of transplant				
Kidney ± pancreas	64 (56)	16 (34)	48 (72)	**<0.001**
Heart	18 (16)	14 (30)	4 (6.0)	**<0.001**
Liver	17 (15)	5 (11)	12 (18)	0.28
Lung	15 (13)	12 (26)	3 (4.5)	**0.002**
Allograft rejection episodes				
Number of acute rejections	1 (0–14)	2 (0–14)	1 (0-5)	**0.02**
Acute before PTLD, yes	69 (61)	32 (68)	37 (55)	0.17
Chronic before PTLD, yes	18 (16)	7 (15)	11 (16)	0.83
Graft failure before PTLD	20 (18)	7 (15)	13 (19)	0.53
Retransplantation				
Before PTLD	13 (11)	6 (13)	7 (10)	0.70
Not before PTLD or never	101 (89)	41 (87)	60 (90)	
Immunosuppression (besides ATG)				
Corticosteroids	114 (100)	47 (100)	67 (100)	NS
Calcineurin inhibitors	108 (95)	46 (98)	62 (93)	0.40
Azathioprine	89 (78)	36 (77)	53 (79)	0.75
Mycophenolic acid	25 (22)	12 (26)	13 (19)	0.44
Muromonab-CD3 (OKT-3)	15 (13)	8 (17)	7 (10)	0.31
Other[a]	8 (7)	6 (13)	2 (3)	0.06
Early/late-onset PTLD				
< 1-year post-SOT	34 (30)	19 (40)	15 (22)	**0.04**
> 1-year post-SOT	80 (70)	28 (60)	52 (78)	
Time from last SOT to PTLD, years	4.0 (0.1–25.7)	2.0 (0.2–17.5)	6.6 (0.1–25.7)	**0.002**
PTLD subtype				
Polymorphic + nondestructive	9 (8)	8 (17)	1 (1.5)	**0.004**
DLBCL	52 (46)	21 (45)	31 (46)	0.87
Germinal center	11 (23)	0 (0)	11 (39)	**0.001**
Non-germinal center	37 (77)	20 (100)	17 (61)	
Burkitt lymphoma	5 (4)	2 (4.3)	3 (4.5)	1.00
T cell monomorphic	15 (13)	2 (4.3)	13 (19)	**0.02**
Hodgkin-type	5 (4)	1 (2.1)	4 (6.0)	0.65
Lymphoma, unclassifiable	28 (25)	13 (28)	15 (22)	0.48
EBV-status of PTLD	101 (89)			
EBER+	57 (56)	33 (80)	24 (40)	**<0.001**
EBER-	44 (44)	8 (20)	36 (60)	
EBV serostatus of recipient pretransplant	67 (59)			
EBV+	45 (67)	22 (65)	23 (70)	0.66
EBV-	22 (33)	12 (35)	10 (30)	
Localization of PTLD				
Nodal, only	25 (22)	11 (23)	14 (21)	0.75
Extranodal	89 (78)	36 (77)	53 (79)	
Gastrointestinal tract	28 (25)	10 (21)	18 (27)	0.50
Allograft	20 (18)	15 (32)	5 (7.5)	**<0.001**
Blood/bone marrow	12 (11)	3 (6.4)	9 (13)	0.35
Liver[b]	13 (11)	7 (15)	6 (9.0)	0.33
Central nervous system	10 (8.8)	3 (6.4)	7 (10)	0.52
Lung[c]	12 (11)	4 (8.5)	8 (12)	0.76
Presentation stage (Ann Arbor)				
I–II	54 (47)	25 (53)	29 (43)	0.30
III–IV	60 (53)	22 (47)	38 (57)	
Performance status (ECOG)				
0–1	77 (68)	29 (62)	48 (72)	0.26
2–4	37 (32)	18 (38)	19 (28)	
B symptoms at diagnosis	109 (96)			
Yes	55 (50)	24 (56)	31 (47)	0.37
No	54 (50)	19 (44)	35 (53)	
Serum LDH at diagnosis	81 (71)			
Normal	26 (32)	10 (34)	16 (31)	0.73
Elevated	55 (68)	19 (66)	36 (69)	
Age-adjusted IPI	101 (89)			
0–1 points	56 (55)	24 (59)	32 (53)	0.61
2–3 points	45 (45)	17 (41)	28 (47)	
PTLD treatment				
RIS only	15 (13)	9 (19)	6 (9.0)	0.11
Chemotherapy	70 (61)	26 (55)	44 (66)	0.26

(*continued*)

Table 1. Continued.

		N (%) or median (range, min-max)		
	All	ATG	No ATG	*p* Value
Rituximab	19 (17)	5 (11)	14 (21)	0.15
Radiation	20 (18)	9 (19)	11 (16)	0.71
Surgery	26 (23)	14 (30)	12 (18)	0.14
None	9 (7.9)	2 (4.3)	7 (10)	0.30
Treatment response[d]				
Complete	64/101 (63)	32/44 (73)	32/57 (56)	0.09
Calendar year of PTLD				
1980–1999	62 (54)	31 (66)	31 (46)	**0.04**
2000–2006	52 (46)	16 (34)	36 (54)	

[a]Other immunosuppressive regimens include basiliximab, daclizumab, methotrexate, and cyclophosphamide. [b]PTLD in a transplanted liver is reported as allograft and not liver, [c]PTLD in a transplanted lung is reported as allograft and not lung, [d]Treatment response on first and secondary treatment, patients who did not receive treatment ($n = 9$) and with missing data ($n = 4$) were excluded. ATG: antithymocyte globulin; PTLD: post-transplant lymphoproliferative disorder; NS: not significant; SOT: solid organ transplantation; DLBCL: diffuse large B cell lymphoma; EBER: Epstein-Barr virus-encoded RNA; ECOG: Eastern Cooperative Oncology Group; LDH: lactate dehydrogenase; IPI: International Prognostic Index; RIS: reduction of immunosuppression.
Statistically significant *p* values are highlighted in bold.

We speculate that the PTLDs in the ATG group may have a different pathogenesis than the PTLDs in the no ATG group. We have previously reported that induction therapy with ATG was associated with a lower frequency of regulatory T cells in the microenvironment of the PTLD [24]. However, it was especially patients given ATG as rejection therapy who had a better outcome. One may speculate that heavily immunosuppressed patients are more prone to develop nondestructive and polymorphic PTLD (as opposed to monomorphic PTLD) and that they may respond better to certain therapies, for example reduced immunosuppression. There was a trend that the PTLDs occurring after ATG therapy responded better to reduction of immunosuppression as only PLTD treatment, but the limited number of patients do not permit definitive conclusions. This better response may be due to a higher proportion of polymorphic PTLD in the ATG group, since polymorphic PLTD are reported to respond better to reduction of immunosuppression than monomorphic PTLD [25,26]. However, the better outcome for the ATG group is not due to improved lymphoma therapy with the introduction of rituximab and better supportive care after the year 2000, since the majority of the PTLDs diagnosed between 2000 and 2006 were found in patients who had not received ATG.

Naturally the distribution of PTLD subtypes in the groups may affect survival. T-cell PTLDs, which have a particularly poor prognosis [2,20], were more common in the no ATG group and this may in part explain the inferior survival in this group. We also found that the non-germinal center type of DLBCL was more common in the ATG group compared with the no ATG group. However, cell-of-origin of DLBCL post-transplant does not affect overall survival as shown by us and others previously [2,27], but it suggests that pathogenesis may differ in the development of PTLDs in the two groups.

Gene expression profiling, next-generation sequencing, and microRNA profiles have shown that EBV + and EBV- PTLD constitute two distinct molecular-genetic subgroups of PTLD that are more important than the cell-of-origin classification of DLBCL post-transplant [28,29]. For example, EBV + PTLDs are reported to have fewer genetic aberrations than EBV- PTLDs [29–31]. Also tumor microenvironment differs between EBV + and EBV- PTLD [30,32]. A majority of the PTLDs arising after ATG therapy in our present study were EBV + and therefore naturally shared several features typical for EBV + PTLDs: early-onset after transplantation, tendency to involve the graft, larger proportion of polymorphic PTLD and non-germinal center subtype of DLBCL, and lower proportion of T-cell PTLDs. However, EBV-status was not associated with overall survival in different adjusted Cox proportional hazards regression models in our case series, whereas prior ATG treatment was. The finding that EBV-status of PTLD lacks prognostic impact has been reported by us and others previously [2,3,14,15,18,33].

Immunosuppressive agents have seldom been included in analyses of prognostic factors for PTLD [14,15,18] but in the studies that have done this, ATG was not associated with survival [5,16]. In a study of 344 PTLDs following renal transplantation in the United States, use of muromonab-CD3 was associated with inferior survival, whereas ATG was not associated with survival [5]. In a study of 500 PTLDs after renal transplantation in France, neither muromonab-CD3 nor ATG was associated with survival [16].

Even though this case series is nationwide and comprises PTLDs that arose during 26 years, the material is still rather small and the results may be uncertain. In addition, the use of ATG is probably more prudent today compared with during this study period. Moreover, the awareness of and treatment for PTLD has improved in recent years. Furthermore, our finding that patients who developed PTLD after ATG therapy have a better outcome should not be interpreted as a recommendation to increase the use of ATG for induction or rejection treatment. ATG is definitely an important risk factor for PTLD and the best for the patient is of course to avoid development of PTLD. However, awareness that the patient has received prior ATG might influence the tailoring of the therapy for PTLD.

In conclusion, ATG therapy prior to PTLD development, especially when given as rejection therapy, is an independent prognostic factor for superior overall survival after PTLD diagnosis. This may in part be due to a different composition of PTLD subtypes in ATG-treated compared with non-ATG-treated patients and suggests a different tumor biological mechanism.

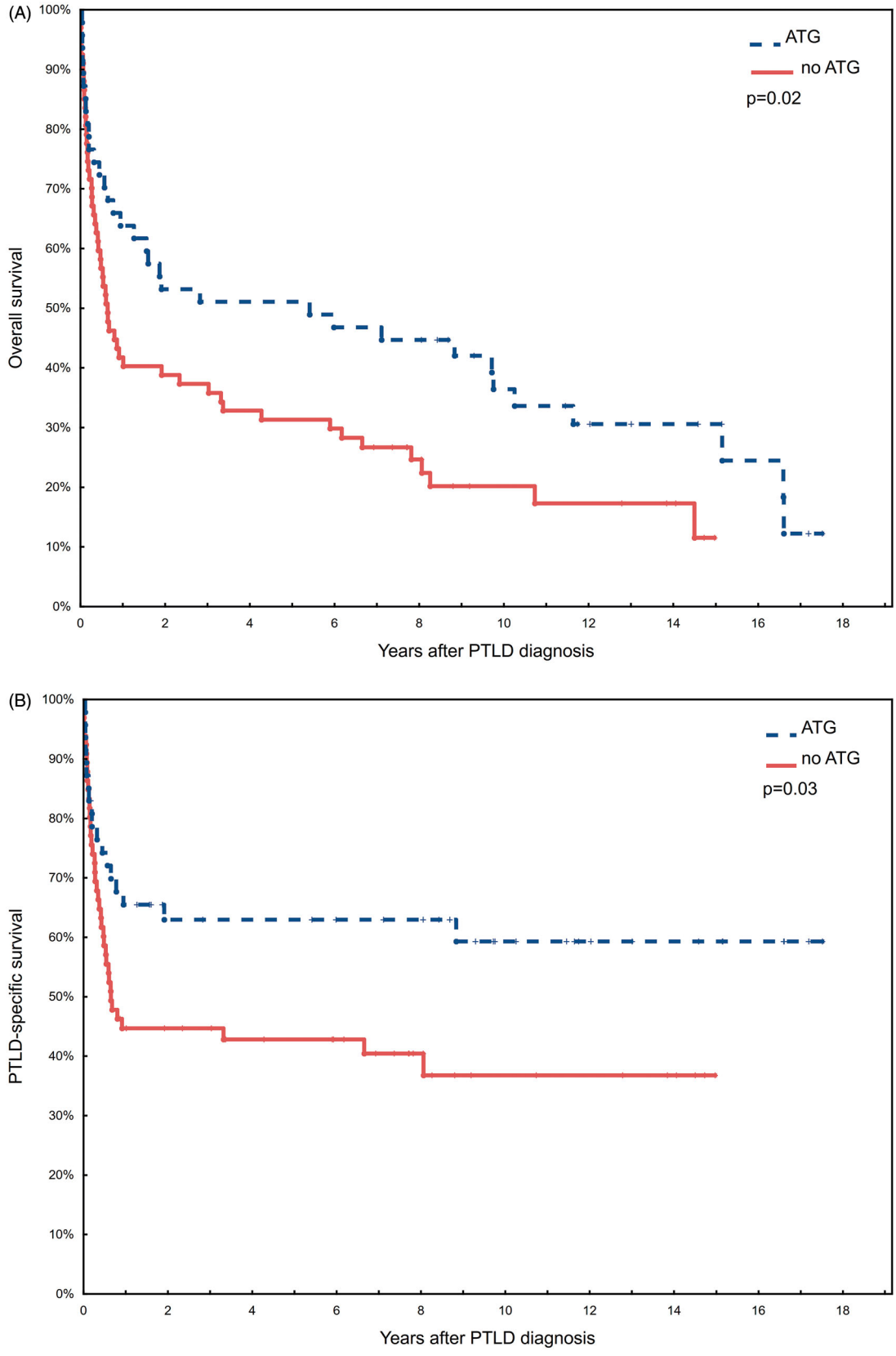

Figure 1. Overall (A) and disease-specific (B) survival after diagnosis of PTLD in patients who did or did not receive previous therapy with antithymocyte globulin (ATG). Overall survival after PTLD in patients who received ATG solely as rejection therapy compared with patients who received ATG as induction therapy, including six patients who received ATG both for induction and rejection (C).

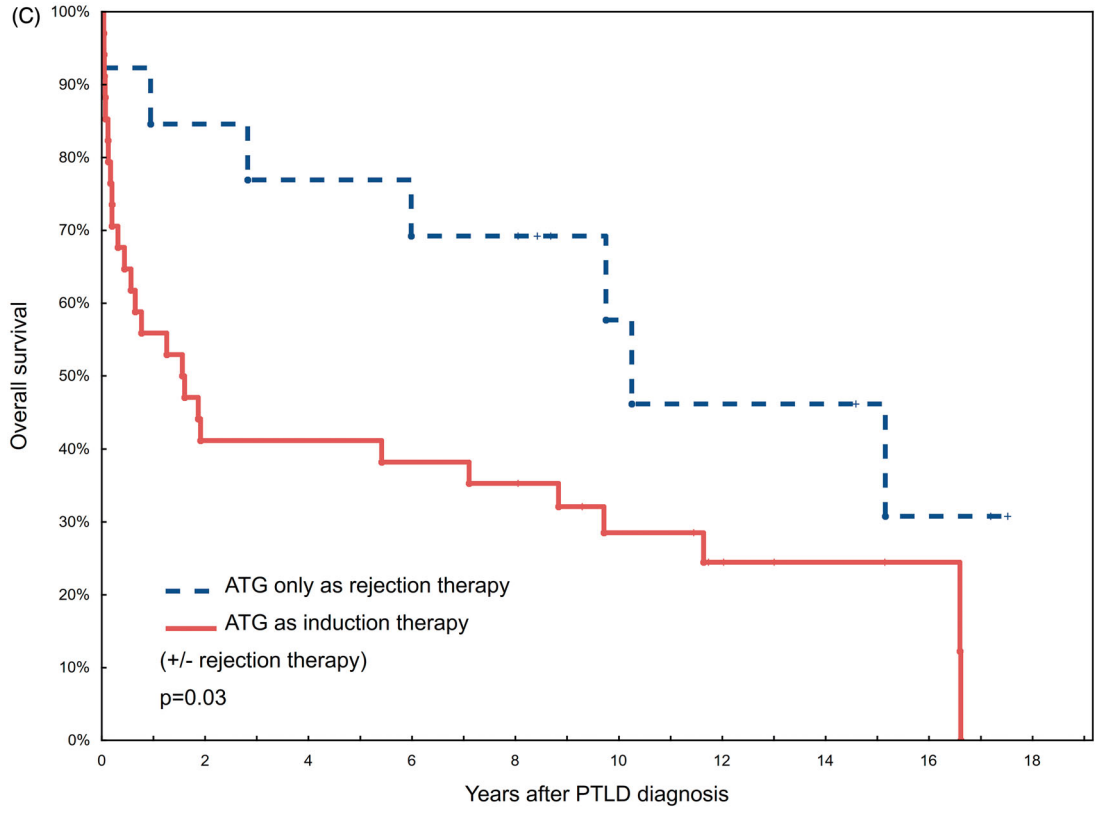

Figure 1. Continued.

Table 2. Analysis of prognostic factors for overall survival in PTLD after solid organ transplantation by Cox proportional hazards regression model.

	Unadjusted		Adjusted	
Factor	Hazards ratio (95% CI)	p	Hazards ratio (95% CI)	*p*
Age at PTLD diagnosis	1.03 (1.01–1.04)	**<0.001**	1.08 (1.05–1.11)	**<0.001**
Gender, male (vs. female)	0.76 (0.50–1.16)	0.20		
Type of transplant				
Lung	0.46 (0.22–0.96)	**0.04**	0.56 (0.19–1.64)	0.29
Liver	0.58 (0.31–1.09)	0.09		
Heart	1.49 (0.86–2.56)	0.16		
Kidney +/− pancreas	1.55 (1.00–2.39)	0.05		
Type of PTLD				
Polymorphic and nondestructive	0.55 (0.22–1.36)	0.20		
Monomorphic B cell	1.00 (0.64–1.57)	0.98		
Monomorphic T cell	2.72 (1.53–4.83)	**<0.001**	2.55 (1.13–5.77)	**0.02**
Hodgkin-type	0.86 (0.27–2.72)	0.80		
B symptoms, yes (vs. no)	1.97 (1.27–3.05)	**0.002**	3.44 (1.78–6.65)	**<0.001**
Performance status, ECOG 0-1 (vs. 2-4)	0.51 (0.33–0.79)	**0.003**	0.36 (0.19–0.70)	**0.003**
Stage I-II (vs. III-IV)	0.78 (0.51–1.20)	0.26	1.73 (0.88–3.39)	0.11
S-LDH, elevated (vs. normal)	1.79 (1.00–3.22)	0.05	2.30 (1.14–4.63)	**0.02**
ATG therapy, ever (vs. never)	0.60 (0.38–0.94)	**0.02**	0.42 (0.21–0.83)	**0.01**
Muromonab-CD3, ever (vs. never)	0.99 (0.54–1.82)	0.97		

CI: confidence interval; PTLD: post-transplant lymphoproliferative disorder; ECOG: Eastern Cooperative Oncology Group; LDH: lactate dehydrogenase; ATG: antithymocyte globulin.
Statistically significant *p* values are highlighted in bold.

Disclosure statement

DM has received honoraria from Roche, Merck, Bristol-Myers Squibb, and Takeda. The other authors report no conflict of interest.

ORCID

Amelie Kinch http://orcid.org/0000-0003-3420-8590
Daniel Molin http://orcid.org/0000-0002-9646-7283
Karlis Pauksens http://orcid.org/0000-0003-2626-7574
Gunilla Enblad http://orcid.org/0000-0002-0594-724X

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