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A contemporary analysis of induction immunosuppression in pediatric lung transplant recipients

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Summary

There is an increasing trend in the use of induction immunosuppression in children undergoing lung transplantation (LTx). To evaluate the effect of this practice on survival, the *United Network for Organ Sharing* (UNOS) was queried from 1987 to 2012, restricting analysis to transplant patients 6–17 years old from 2001 to 2012, who received no induction (NONE) or induction (INDUCED) with the contemporary agents of basiliximab, alemtuzumab, thymoglobulin, antilymphocyte globulin (ALG), or antithymocyte globulin (ATG). Of 23 951 lung transplants, 330 met inclusion criteria with 177 (54%) being INDUCED. Of the INDUCED agents, 121 (68%) were basiliximab, 3 (2%) alemtuzumab, and 53 (30%) ALG/ATG/thymoglobulin. The mean patient age was 13.6 (SD = 3.2) and 14 (SD = 3.0) years for the INDUCED and NONE groups, respectively. The median survival in the INDUCED group was 77.4 months (95% CI: 46.1, 125.6) compared with 50.8 months (95% CI: 42.9, 61.3) for the NONE (log-rank *P*-value = 0.3601). The most common cause of death was due to allograft failure or pulmonary complications with only one patient dying from post-transplant lymphoproliferative disorder. The estimated hazard ratio for INDUCED versus NONE was 0.859 (95% CI: 0.620, 1.191; *P* = 0.3618); there were no significant confounders or effect modifiers among the demographic and clinical variables. In conclusion, antibody-based induction immunosuppression with contemporary agents had a trend toward a protective, but not statistically significant, effect in 6- to 17-year-old patients.

Introduction

Lung transplantation (LTx) is recognized as a worldwide standard treatment for children with a broad spectrum of advanced pulmonary disorders of various etiologies depending on the age of the patient [1]. There is a clear separation of the indications for LTx in children at 6-years of age with vast difference in the primary reasons why pediatric lung transplant are performed. For children 6 years old and older, the more common indications include cystic fibrosis (CF), idiopathic pulmonary arterial hypertension (IPAH), obliterative bronchiolitis (OB), pulmonary fibrosis (PF), and idiopathic pulmonary fibrosis (IPF) [1].

As in adult patients, children are afflicted with bronchiolitis obliterans syndrome (BOS) as the primary cause of chronic rejection, which limits long-term survival for those patients who live beyond 1 year after LTx [1]. The key clinical feature of BOS is a decline in pulmonary function and onset of airway obstruction with a reduction in forced expiratory volume in 1 s (FEV_1) that is progressive and does

not respond to bronchodilators [2,3]. The frequency and severity of acute cellular rejection (ACR) are the most important risk factors in the subsequent development of BOS in adult patients after LTx [4–9], with even grade A1 rejection being a factor for adults [4]. The impact of ACR upon the development of BOS in children is not as clear due to a limited number of research studies. In pediatric lung transplant recipients, Benden *et al.* [10] found that 1–2 episodes of grade A1 ACR did not increase the risk for BOS, but a single episode of grade A2 ACR was associated with twice the risk for BOS within 1 year of LTx.

The role of induction immunosuppression in LTx is varied in adult and pediatric patients. In the pediatric population, due to a smaller national incidence and center practice variability, the impact is even more unclear. There has been an upward trend in the use of various induction immunosuppressive agents in children [1,11]. Based on current published findings, it is clear that the incidence of ACR is lower during the first year after LTx in those patients who received induction therapy, including children [5,12,13]. Furthermore, adult lung recipients who received induction therapy had statistically significant higher graft and patient survival rates than those patients who did not [14], but no study has investigated the impact of induction therapy upon survival after pediatric LTx. Therefore, we sought to evaluate the effect of contemporary induction immunosuppression on survival in recipients between 6 and 17 years of age after LTx.

Methods

We retrospectively evaluated the outcome of pediatric lung transplant recipients whose data were registered in the Organ Procurement and Transplant Network (OPTN) Standard Transplant Analysis and Research (STAR) Database [15]. With the National Organ Transplant Act of 1984, the OPTN was established by the United States Congress. The United Network for Organ Sharing (UNOS) is a private, nonprofit organization that administers the OPTN under a federal contract. The STAR database is administrated through UNOS/OPTN as overseen by the United States Department of Health and Human Services. The UNOS/OPTN STAR database maintains data elements reflecting donor characteristics (e.g., donor mechanism of death, donor age, donor gender), pretransplant recipient characteristics (e.g., indication for transplantation, recipient age, recipient gender), and post-transplant recipient characteristics and outcomes (i.e., length of stay, recipient survival, development of postoperative complication) for solid organ transplants from 1987 to present. Data are entered at the time of a patient's listing, and again at their time of transplantation. The data are extracted by the individual centers and submitted as aggregate data to the OPTN United States Scientific Registry of Transplant Recipients (SRTR), which then collates and manages the data per the above-referenced contract.

This retrospective review was approved by The Ohio State University Wexner Medical Center Institutional Review Board with a waiver of the need for individual consent. For purposes of this analysis, we queried the UNOS/OPTN thoracic database for all lung transplants from January 1987 to November 2012. Our inclusion and exclusion criteria are listed in Table 1. We grouped the lung transplant recipients into either no induction (NONE) or induction with contemporary agents of basiliximab, alemtuzumab, thymoglobulin, ALG, or ATG (INDUCED). The primary endpoint was overall survival after transplant for patients in the INDUCED versus NONE groups.

All demographic characteristics were summarized for the INDUCED and NONE groups separately, and Kaplan–Meier estimates of the survival function were produced to assess crude differences in overall survival. The univariable (unadjusted) hazard ratio (HR) and 95% confidence interval (CI) for INDUCED versus NONE was calculated using a Cox proportional hazards model. Next, we checked for the presence of significant confounders or effect modifiers to the relationship between induction and overall survival using a risk factor modeling approach [16], excluding variables with 30% missing data or more from consideration. Using a forward selection approach, each variable was added to the unadjusted model one at a time and the percentage change in the hazard ratio for induction from the univariable model was calculated. Variables were to be considered confounders if the addition of that variable to the model caused at least a 15% change or greater in the hazard ratio. Next, all two-way interactions between each covariate and the induced indicator were calculated; those with $P < 0.01$ were considered significant effect modifiers. The proportional hazards assumption was assessed graphically;

Table 1. Study cohort inclusion/exclusion criteria.

Step	*N*
All lung transplants	23 951
First transplant, excluding those with retransplants or multiple transplants on the same day	23 023
Survival status is present, patient and graft survival time is greater than 0	22 748
Recipient age 6–17	774
Cadaveric donors only	690
Transplants occurring in 2001 or later	403
Excluding patients who could be categorized in more than one antibody-based induction agent or on OKT3, Zenapax, ANTIICAM1, ANTILFA1, DAB486IL2, NRATGNRATS, OKT4, T10B9, or XOMAZYMECD5	330

no serious deviations were observed. All analyses were performed using SAS/STAT software, version 9.2 (SAS Institute Inc., Cary, NC, USA).

Results

Study Cohort

Of the 23 951 lung transplants identified in the database, 330 met our inclusion criteria. A total of 54% (177/330) of patients received an antibody-based induction agent (INDUCED) (Table 2). Among those, the majority (68%) received basiliximab (Table 2).

A summary of demographic and clinical characteristics by induction status is shown in Table 3. Overall, the indications for transplantation were categorized as 68% CF, 10% IPF/OB/PF, 9% IPAH, and 12% other, and were similar between INDUCED and NONE patients. The mean patient age was 13.6 years (SD = 3.2 years) for the INDUCED group and 14 years (SD = 3.0 years) for the NONE group. The largest number of donor organs was ischemic for 4–6 h (47%). The majority of both recipients (77%) and donors (54%) were Caucasian. Donor to recipient race matching took place in 51% of cases. The majority of both recipients (58%) and donors (51%) were female. While a majority of the demographic factors were similar between the INDUCED and NONE groups, a higher proportion of patients in the INDUCED group had diabetes compared with the NONE group (28% vs. 19%, respectively).

Survival

Overall, 44% (146/330) of patients died during the post-transplant period; 67 (38%) and 79 (52%) of the INDUCED and NONE groups, respectively. The median follow-up time for the INDUCED group was 24.2 months as compared with 36.3 months for the NONE group. Kaplan–Meier estimates of the survival function for INDUCED versus NONE are illustrated in Fig. 1. The median survival in the INDUCED group was 77.4 months (95% CI: 46.1, 125.6) as compared to 50.8 months (95% CI: 42.9, 61.3) for the no induction group (log-rank *P*-value=0.3601) (Table 4, Fig. 1). In both the INDUCED and NONE groups, 25% were treated for ACR with 23% (75/330) of the data uncoded (data not shown). Table 5 shows the causes of death in both the INDUCED and NONE groups. The most common cause of death was allograft failure or pulmonary related complications with other/unknown causes being the next most common. More importantly, there was only one death reported due to malignancy from post-transplant lymphoproliferative disorder (PTLD), which actually occurred in a patient in the NONE group.

Table 2. Antibody-based induction agent status.

Antibody-based induction agent ("INDUCED")	*N* (%)
No	153 (46%)
Yes	177 (54%)
Basiliximab	121 (68%)
Alemtuzumab	3 (2%)
ALG/ATG/Thymoglobulin	53 (30%)

Cox proportional hazards modeling for INDUCED (yes versus no)

The univariable (unadjusted) hazard ratio for INDUCED versus NONE was less than one, but not statistically significant at the 0.05 level (estimated HR = 0.859; 95% CI: 0.620, 1.191; $P = 0.3618$) (Table 6). All variables listed in Table 3 with <30% missing data were assessed for confounding by calculating the change in the univariable hazard ratio after adding each variable to the model one at a time (Table 7). The majority of variables examined elicited <5% change in the univariable hazard ratio when added to the model. The maximum observed change in the hazard ratio was seen when ischemic time was added to the model (−5.7%). Still, the hazard ratio for INDUCED in the model containing ischemic time was not statistically significant ($P = 0.2358$). In fact, by adding all variables into the model with <10% missing data, the hazard ratio for INDUCED only changed by <1% from the univariable hazard ratio, moving closer to 1 (estimated HR = 0.863; 95% CI: 0.580, 1.284; $P = 0.4677$); therefore, we did not include any of the variables as confounders in the model. We also assessed the presence of effect modification by considering all two-way interactions with INDUCED (Table 7); none of the variables met the criterion for effect modification (interaction $P < 0.01$), although the interaction between donor/recipient race match and induction was borderline significant ($P = 0.0354$).

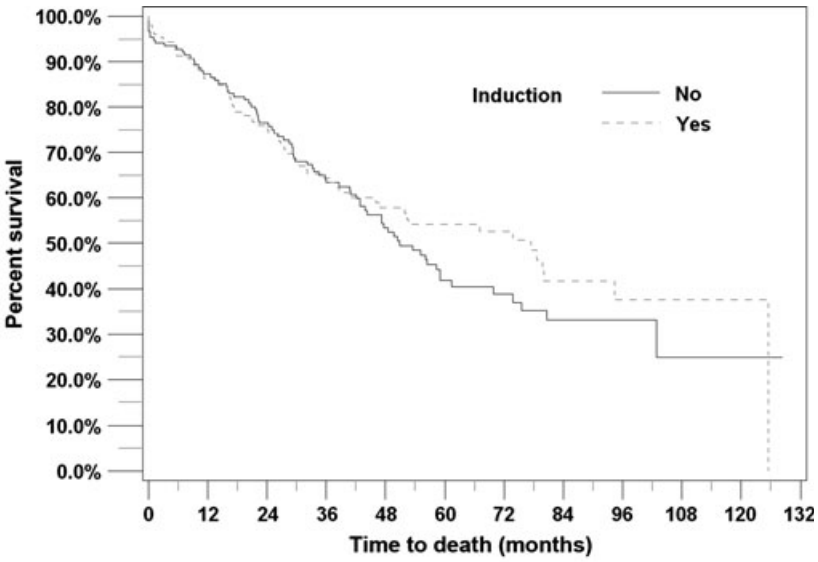
For transplants with no donor/recipient race matching, the hazard ratio for INDUCED was 1.26 (95% CI: 0.777, 2.049; $P = 0.3479$) (Table 8). In contrast, for transplants with donor/recipient race matching, the hazard ratio for INDUCED was 0.612 (95% CI: 0.384, 0.977; $P = 0.0396$) (Table 7). However, due to the majority of donors and recipients being Caucasian, almost 90% of all donor/recipient race matches were Caucasian. Of the 254 total Caucasian recipients, 139 (55%) of the donors were also Caucasian, compared with only 5/17 (29%) African-American recipients matched with African-American donors. Unfortunately, due to the small numbers of non-Caucasian donors and recipients, we are unable to investigate any potential differences in donor/recipient race matching between recipients of different racial groups.

Table 3. Demographics by antibody-based induction agent status.

Variable	Level	Antibody-based induction agent		
		No (n = 153)	Yes (n = 177)	Total (n = 330)
Diagnosis	Cystic fibrosis	101 (66%)	125 (71%)	226
	IPAH	15 (10%)	15 (8%)	30
	IPF/OB/PF	21 (14%)	13 (7%)	34
	All Other	16 (10%)	24 (14%)	40
Ischemic time group	Missing	19 (12%)	12 (7%)	31
	<4 h	25 (16%)	18 (10%)	43
	4–6 h	67 (44%)	87 (49%)	154
	>6 h	42 (27%)	60 (34%)	102
Recipient race	Caucasian	112 (73%)	142 (80%)	254
	African	9 (6%)	8 (5%)	17
	American	32 (21%)	27 (15%)	59
	Other			
Donor race	Caucasian	91 (59%)	89 (50%)	180
	African	25 (16%)	43 (24%)	68
	American	37 (24%)	45 (25%)	82
	Other			
Donor/Recipient race match	No match	69 (45%)	98 (55%)	167
	Match	84 (55%)	79 (45%)	163
Recipient gender	F	92 (60%)	98 (55%)	190
	M	61 (40%)	79 (45%)	140
Donor gender	F	73 (48%)	94 (53%)	167
	M	80 (52%)	83 (47%)	163
Donor/Recipient gender match	No match	71 (46%)	84 (47%)	155
	Match	82 (54%)	93 (53%)	175
Serum creatinine at time of transplant	Missing	8 (5%)	1 (1%)	9
(≤2 mg/dl vs. >2 mg/dl)	Creatinine ≤ 2	141 (92%)	172 (97%)	313
	Creatinine > 2	4 (3%)	4 (2%)	8
Chronic steroid use at time of transplant	Missing	12 (8%)	5 (3%)	17
	N	89 (58%)	116 (66%)	205
	Y	52 (34%)	56 (32%)	108
Diabetes	Missing	2 (1%)	2 (1%)	4
	N	122 (80%)	126 (71%)	248
	Y	29 (19%)	49 (28%)	78
CMV match	Missing	6 (4%)	3 (2%)	9
	No match	85 (56%)	105 (59%)	190
	Match	62 (41%)	69 (39%)	131
Recipient age at time of transplant	No. missing	0	0	0
	Mean (SD)	14 (3.0)	13.6 (3.2)	13.8 (3.1)
	(min, max)	(6.0, 17.0)	(6.0, 17.0)	(6.0, 17.0)
Calculated Recipient BMI	No. missing	4	0	4
	Mean (SD)	18.1 (4.2)	17.3 (3.7)	17.7 (3.9)
	(min, max)	(5.1, 32.3)	(12.0, 44.9)	(5.1, 44.9)
Serum Creatinine at Time of Transplant (mg/dl)	No. missing	8	1	9
	Mean (SD)	0.7 (1.1)	0.7 (1.6)	0.7 (1.4)
	(min, max)	(0.2, 12.0)	(0.1, 15.0)	(0.1, 15.0)
Total Bilirubin at Time of Transplant (mg/dl)	No. missing	19	29	48
	Mean (SD)	0.6 (1.0)	0.6 (2.1)	0.6 (1.7)
	(min, max)	(0.1, 6.9)	(0.1, 25.3)	(0.1, 25.3)

Discussion

Induction therapy is an extreme prophylactic immunosuppression given perioperatively in hopes to prevent ACR in the postoperative period [17,18]. A common practice is restricted use of induction therapy in children due to the potential risk of PTLD and associated complications; however, these data demonstrate low risk for the development of severe complications in the 6- to 17-years-old patient population with the currently available antibody-based



Number at Risk							
Group	Time (Months)						
	0	24	48	72	96	120	144
No Induction	153	103	56	22	7	1	0
Induction	177	91	50	32	9	1	0

Figure 1 Kaplan–Meier estimates of postlung transplant survival in recipients who received contemporary antibody-based induction immunosuppression or not (Log-rank *P*-value = 0.3601). The number at risk over time is presented in the table below the *x*-axis.

Table 4. Median survival times with 95% CIs by induction status.

Group	*N*	Median survival time (Months)	95% CI
INDUCED: No	153	50.8	(42.9, 61.3)
INDUCED: Yes	177	77.4	(46.1, 125.6)

Table 5. Cause of death between patients who did not receive antibody-based induction agent (NONE) and those who did (INDUCED).

	Antibody-based induction agent		
Cause of death	No (*n* = 79)	Yes (*n* = 67)	Total (*n* = 146)
Pulmonary/Allograft failure	47 (59%)	27 (40%)	74 (51%)
Unknown/Other*	20 (25%)	22 (33%)	42 (29%)
Infection	8 (10%)	13 (19%)	21 (14%)
Cardiovascular	3 (4%)	5 (7%)	8 (5%)
Malignancy†	1 (1%)	0 (0%)	1 (1%)

*Other included cerebral hemorrhage, brain anoxia, gastrointestinal hemorrhage, liver failure, renal failure, and multiple organ failure.
†Malignancy was post-transplant lymphoproliferative disorder.

Table 6. Univariable Cox proportional hazards model for overall survival: INDUCED versus NONE.

Comparison	Estimated HR	95% CI	*P*-value
INDUCED versus NONE	0.859	(0.620, 1.191)	0.3618

induction agents. Due to limited research involving pediatric patients, the known clinical benefit for induction therapy with LTx in younger patients has been variable.

There is evidence that induction therapy reduces ACR in pediatric patients as seen when Goldfarb *et al.* [12] reported a reduction in ACR incidence of ACR in 18 children during the 6 months after LTx with ATG dosing prior to donor reperfusion; however, the long-term benefit was not defined. More recently, significant improvement in 5-year survival was seen with ATG induction therapy in CF patients, with the cohort ranging in age between 16 and 36 years of age [19]. Despite the lack of studies demonstrating a direct benefit and no existing consensus on the use of induction therapy in pediatric LTx, an increased use of induction agents has occurred [1,11].

In our analysis of the UNOS/OPTN STAR database, we focused on contemporary therapies, so we limited our

Table 7. Assessing confounding (% change in HR) and effect modification (interaction *P*-value) in the Cox model for overall survival by induction status (INDUCED).

Variable	HR for INDUCED with variable in the Model	% Change in HR for INDUCED*	Interaction *P*-value
Diagnosis	0.838	−2.4	0.0595
Ischemic Time Group	0.867	0.9	0.3227
Recipient Race	0.883	2.8	0.4172
Donor Race	0.874	1.8	0.6021
Donor/Recipient race match	0.864	0.6	0.0354
Recipient gender	0.858	−0.1	0.4561
Donor gender	0.852	−0.8	0.3195
Donor/Recipient gender match	0.859	<0.1	0.4688
Serum creatinine at time of transplant (≤2 mg/dl vs. >2 mg/dl)	0.870	1.3	0.8485
Chronic steroid use at time of transplant	0.872	1.5	0.5416
Diabetes	0.856	−0.4	0.7070
CMV match	0.869	1.2	0.1759
Recipient age (Quartiles)	0.888	3.4	0.3345
Recipient age at time of transplant	0.884	2.9	0.3135
Calculated recipient BMI	0.887	3.3	0.1285
Ischemic time (h)	0.810	−5.7	0.8603
Serum creatinine at time of transplant (mg/dl)	0.872	1.5	0.4319
Total bilirubin at time of transplant (mg/dl)†	0.911	6.1	0.2240

*Univariable HR for INDUCED versus NONE = 0.805.
†Model contained at least 10% more missing data compared with univariable model.

Table 8. Estimated hazard ratios and 95% CI from the Cox model for overall survival by induction status (INDUCED), including the interaction with donor/recipient race match.

Donor/ Recipient race match	Comparison	Estimated HR	95% CI	*P*-value
No Match	INDUCED versus NONE	1.262	(0.777, 2.049)	0.3479
Match	INDUCED versus NONE	0.612	(0.384, 0.977)	0.0396

analysis from 2001 and forward. Although there appears to be a trend toward better survival for pediatric patients ages 6–17 who were induced compared with those without induction (median survival = 77.4 months vs. 50.8 months, respectively), the confidence intervals for the median survival times are extremely wide. Neither univariable nor multivariable comparisons reached statistical significance; thus, we cannot conclude that antibody-based induction immunosuppression with contemporary agents in pediatric patients undergoing LTx significantly improves survival. A major factor in the lack of significance in our study is the small sample size. Of the 22 951 lung transplants in the UNOS/OPTN STAR database, only 330 fit our inclusion/exclusion criteria. In addition, only 44% (177) of the 330 patients had a recorded death during the follow-up period. Our sample size is reflected in the wide confidence intervals discussed above. Another possible explanation for our lack of significance is the fact that we combined several induction therapies, which may have different effects on survival, into one overall induction group. While we acknowledge this possibility, due to our sample size we were not able to examine and compare the effects of each induction agent on survival.

We reviewed a list of clinically relevant factors for potential confounding and/or effect modification of the relationship between induction and overall survival, and found only a borderline significant protective effect of antibody-based induction immunosuppression in matched donor–recipient race. While the interpretation of this potential effect modifier is difficult due to the large proportion of Caucasian donors and recipients, we nevertheless find this result intriguing and believe that further investigation of donor/recipient race matching in a more diverse study population would be beneficial.

As in adult patients, it remains to be seen the mechanism by which these induction agents prevent allograft failure and improve patient survival. Specific details of how the induction agent was given was not available for analysis in our study, the existing medical literature clearly demonstrates a lack of consistency in both dosing and timing of the various therapies used [12,20–25]. Therefore, we feel that further research directly comparing induction agents and timing of dosages would provide useful insight and may impart a substantial benefit to pediatric LTx.

There are several additional limitations of the study, which include retrospective collection of data and the lack of granularity of the database. The study is also limited by the challenge of incomplete data as well as the lack of dosage and timing of administration. There is the possibility that data are inaccurately entered. As previously mentioned, our small sample size limits our ability to separate out induction agents and impacts the significance of our results. However, our cohort was multi-institutional, drawing from the largest registry of transplant patients currently available, reducing potential biases observed in single-institution observational studies. Unfortunately, we do not have information on specific transplant centers, which we acknowledge can strongly influence the administration of immunosuppressive induction. Finally, our results are not

applicable for patients under the age of 6, as we excluded them from the analysis due to the significant difference in patient population and the indication for LTx as compared to patients who are 6–17 years of age.

In conclusion, despite the noteworthy differences in median survival times, we found no statistically significant effect of antibody-based induction immunosuppression with contemporary agents in children between 6 and 17 years of age undergoing LTx on overall survival. As LTx becomes more common in children in this age group, clinicians confront decisions about optimal medical management of these complex patients, specifically the use of induction therapy. Based on our findings, severe complications of PTLD is far less of a concern regarding the use of antibody-based induction immunosuppression in pediatric patients as speculated. However, additional research is definitely needed to better define the role of antibody-based induction immunosuppression in pediatric lung LTx.

Authorship

DH: performed the conception and design, acquisition of data, analysis and interpretation of data, and drafted the manuscript; SK: conducted the analysis and interpretation of data, and critically revised the manuscript; AMW: contributed to statistical calculations and analysis and interpretation of data, and revision of the manuscript; AML: was responsible for statistical calculations and analysis and interpretation of data, and revision of the manuscript; PIM: carried out the analysis and interpretation of data, critical revision of the manuscript; MG: performed the analysis and interpretation of data, and critical revision of the manuscript; RSH: performed the conception and design, analysis and interpretation of data, critical revision of the manuscript, and supervision; BAW: contributed the conception and design, acquisition of data, analysis and interpretation of data, and drafting of the manuscript.

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