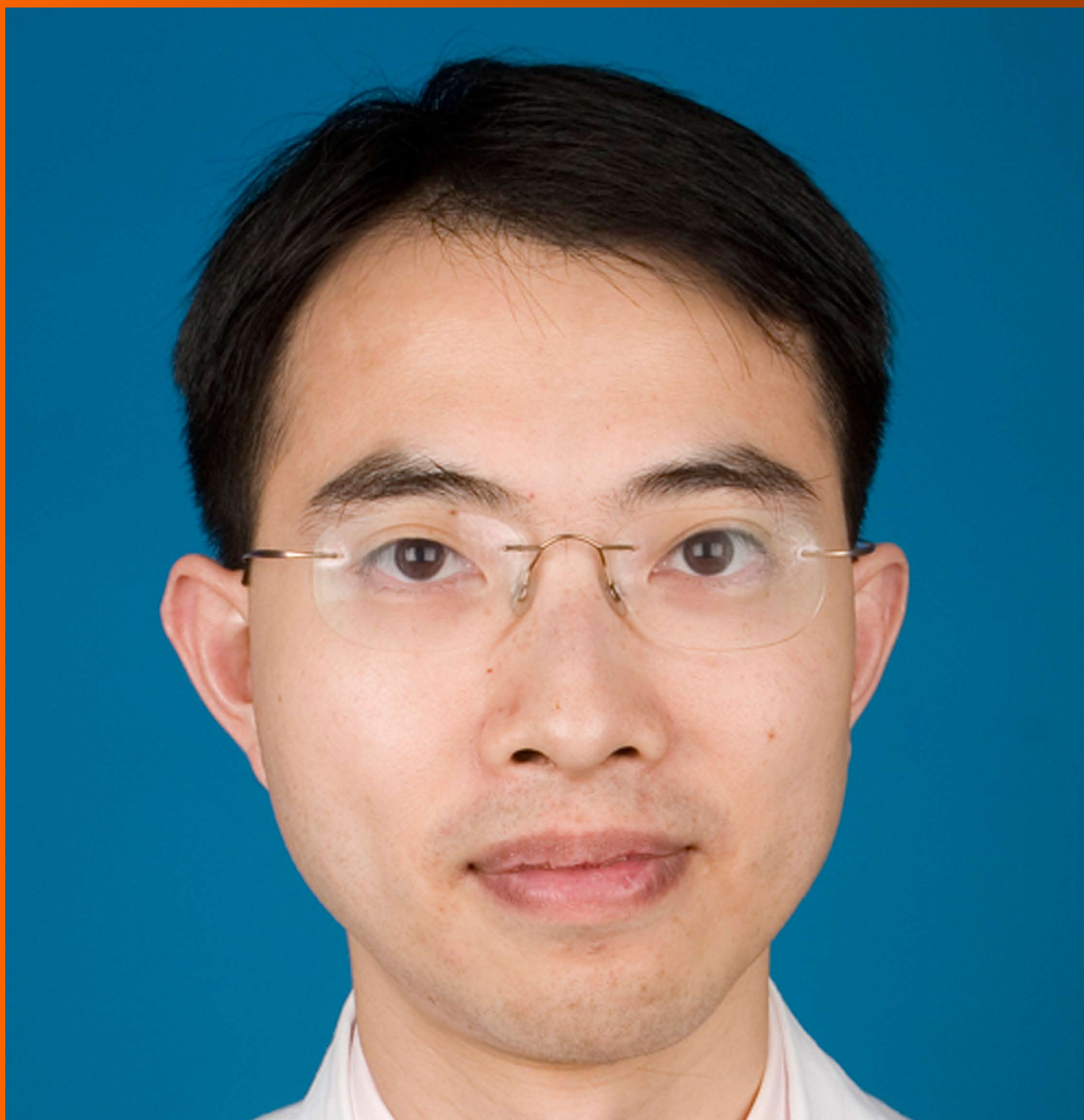


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Peripheral blood stem cell mobilization in multiple myeloma: Growth factors or chemotherapy?

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for eligible patients with multiple myeloma. The optimal collection strategy should be effective in procuring sufficient HSC while maintaining a low toxicity profile. Currently available mobilization strategies include growth factors alone, growth factors in combination with chemotherapy, or growth factors in combination with chemokine receptor antagonists; however, the optimal strategy has yet to be elucidated. Herein, we review the risks and benefits of each approach.

Key words: Multiple myeloma; Stem cell; Mobilization; Growth factors; Chemotherapy

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Core tip: Obtaining an adequate peripheral blood stem cell yield is essential for the successful outcome of autologous hematopoietic stem cell transplant in multiple myeloma. While growth factor mobilization continues to be largely successful, suboptimal collection rates have been noted, particularly as use of novel therapies continue to increase. Chemomobilization remains toxic and has not been associated with better disease control. The newest mobilizing agent, plerixafor, is capable of overcoming suboptimal mobilization even in patients who are at a high risk of mobilization failure. Each mobilization strategy should be selected based on patient specific variables as well as risk factors for mobilization failure.

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Abstract

High-dose therapy followed by autologous hematopoietic stem cell (HSC) transplant is considered standard of care

INTRODUCTION

High-dose therapy followed by autologous hematopoietic

stem cell (HSC) transplant (auto-HCT) is considered standard of care for eligible patients with multiple myeloma (MM). MM remains the most common indication for auto-HCT, accounting for over 6000 transplants in the United States alone in 2013^[1]. Auto-HCT has been shown to prolong progression-free survival and overall survival in patients with MM^[2-4], a benefit that has been maintained even after the availability of immunomodulatory drugs such as thalidomide and lenalidomide^[5,6], and proteasome inhibitors like bortezomib. Mobilization and collection of an optimal number of HSC is a fundamental requirement for auto-HCT. The optimal collection strategy should be effective in procuring sufficient HSC while maintaining a low toxicity profile. Currently available mobilization strategies include growth factors alone, growth factors in combination with chemotherapy, or growth factors in combination with chemokine receptor antagonists; however, the optimal strategy has yet to be elucidated. Herein, we review the data surrounding each approach.

SOURCE OF HSCs

Historically, bone marrow (BM) was used as the sole source of HSC for transplantation^[7,8]. However, the ability to mobilize HSC to peripheral blood (PB) has eliminated the risk of general anesthesia, intubation, and painful aspirations associated with BM harvesting. Peripheral blood stem cell (PBSC) collection can be performed in the outpatient setting with a shorter recovery time. Additionally, use of PBSC reduces time to hematopoietic reconstitution, hospital stay, and need for transfusions^[9-11]. Consequently, PB has largely replaced BM as the source of HSC for auto-HCT^[12].

PBSC DOSE

The number of CD34 expressing mononuclear cells in PBSC collection correlates well with engraftment kinetics and thus is used as a surrogate marker of HSC^[13-16] (Figure 1). A dose of > 2 million CD34⁺ cells per kilogram (cells/kg) is considered the minimum acceptable dose for timely engraftment^[17]. However, larger cell doses have been associated with a more rapid time to platelet and neutrophil recovery^[18,19] and therefore ≥ 3 -5 million CD34 cells/kg is considered an optimal target^[20,21].

PBSC MOBILIZATION APPROACHES

HSC primarily reside in the BM and account for 1%-4% of all mononuclear cells^[13,15,22]. Retention of HSC in the BM is dependent on interactions between cell adhesion molecules on the surface of HSC, such as chemokine receptor 4 and very late antigen 4 (VLA4), and BM stromal factors, such as vascular cell adhesion molecule (VCAM-1) and stromal cell-derived factor-1 (SDF-1)^[23]. Mobilization of HSC from BM to PB is the result of induced chemical disruption of these interactions between HSC and BM stroma. Cytokines,

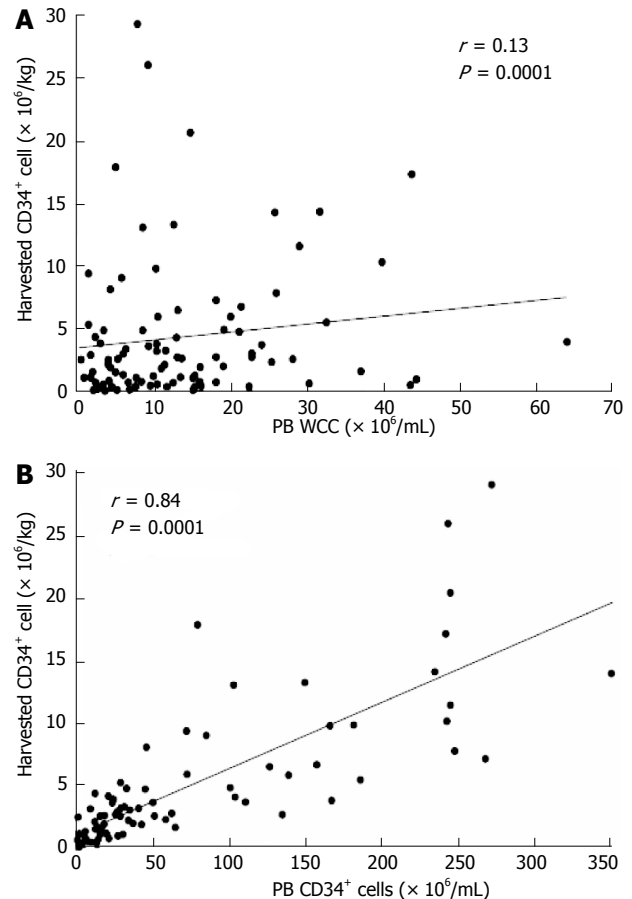


Figure 1 Correlation of harvested CD34⁺ cells counts with white blood cell count and peripheral blood CD34⁺ cell count. A: Correlation of harvested CD34⁺ cells counts with white blood cell count; B: Correlation of harvested CD34⁺ cells counts with peripheral blood CD34⁺ cell count. Reprinted by permission from Macmillan Publishers Ltd: *Bone Marrow Transplant* 1997^[16]. <http://www.nature.com/bmt/index.html>.

such as granulocyte-colony stimulating factor (G-CSF), and chemotherapy drugs like cyclophosphamide play an important role in releasing HSC from their niches in the BM^[23-25] (Figure 2).

Growth factors alone

Historically, growth factors alone have been largely successful in mobilizing an adequate cell yield in MM patients undergoing auto-HCT^[26,27] (Table 1). G-CSF has well established kinetics as well as favorable toxicity and cost profiles^[28-30] but has been associated with suboptimal mobilization in over 20% of MM patients^[31-33]. Data regarding a dose-response relationship between G-CSF and CD34⁺ cell yield is discordant but doses up to 40 μg per kilogram per day ($\mu\text{g}/\text{kg}$ per day) have been studied^[34-36]. A widely accepted G-CSF dose for PBSC mobilization is 10 $\mu\text{g}/\text{kg}$ per day as single or divided doses.

Other growth factors such as granulocyte-macrophage-colony stimulating factor (GM-CSF), pegylated G-CSF, and tbo G-CSF have also been studied for PBSC mobilization in MM patients^[37-42]. When G-CSF was compared to GM-CSF in MM patients, CD34⁺ cell yield was similar between

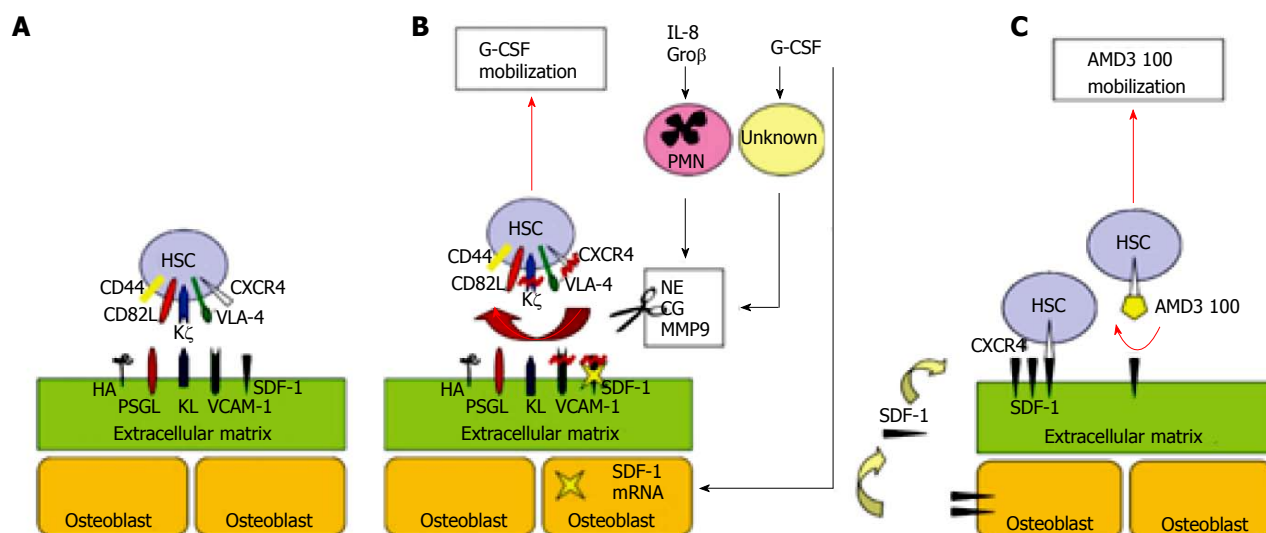


Figure 2 Bone marrow microenvironment (A) at physiologic state and effects of (B) granulocyte colony stimulating factor mobilization and (C) Plerixafor mobilization. Reprinted from *Journal of Cellular Biochemistry*, Vol 99/edition 3, Bruno Nervi, Dan C. Link, John F DiPersio, Cytokines and Hematopoietic Stem Cell Mobilization, 690-705, 2010, with permission from Wiley^[26]. G-CSF: Granulocyte colony stimulating factor; HSC: Hematopoietic stem cell; SDF-1: Stromal cell-derived factor-1; VCAM-1: Vascular cell adhesion molecule.

Table 1 Growth factor mobilization

Ref.	Disease	Collection strategy	n	CD34 ⁺ yield (× 10 ⁶ cell/kg): Median (range)	Failure n (%)
Desikan <i>et al</i> ^[26]	MM	G-CSF 10-16 µg/kg per day	117	6.2 (0.6-34.1)	NR
Kröger <i>et al</i> ^[27]	MM	G-CSF 10-24 µg/kg per day	25	3.8 (0.3-17)	3 (12)
Popat <i>et al</i> ^[31]	MM	G-CSF	302	NR	9%
Pusic <i>et al</i> ^[30]	MM	G-CSF 10 µg/kg per day	384	4.6	24 (6.3)
	NHL HD	G + C	17	8.5	1 (5.9)
Weaver <i>et al</i> ^[34]	BC	G-CSF 10 µg/kg per day	14	0.6 (0.1-2.8)	NR
		G-CSF 20 µg/kg per day	13	1 (0.2-5.2)	
		G-CSF 30 µg/kg per day	14	2.4 (0.6-6.8)	
		G-CSF 40 µg/kg per day	14	1.4 (0.1-4.8)	
Weisdorf <i>et al</i> ^[42]	NHL	GM-CSF 250 µg/m ² per day	16	4.78 (3.02-10.68)	0
	HD	G-CSF 250 µg/m ² per day	15	8.01 (3.17-29)	0
Spitzer <i>et al</i> ^[41]	BC GCT	G-CSF 10 mcg/kg per day	26	21.45 (1.63-182.91)	NR
	NHL HD	G-CSF 10 mcg/kg per day +	24	13.33 (0.56-102.08)	
	MM	GM-CSF 5 mcg/kg per day			
Hosing <i>et al</i> ^[39]	MM	PEG 12 mg × 1	19	8.4 (4.1-15.8)	0
		G-CSF 10 µg/kg per day	8	8.1 (5.17-19.2)	0

MM: Multiple myeloma; G-CSF: Granulocyte colony stimulating factor; NR: Not reported; BC: Breast cancer; NHL: Non-hodgkin's lymphoma; GM-CSF: Granulocyte macrophage colony stimulating factor; HD: Hodgkin's disease; GCT: Germ cell tumor; PEG: Pegylated filgrastim.

the two groups, but GM-CSF-mobilized patients had a longer duration of neutropenia^[43]. *In-vitro* data suggest that combination of G-CSF + GM-CSF may improve PBSC yield^[44,45], but clinical trial data has not found a significant difference in CD34⁺ cell yield or time to hematopoietic recovery with combination therapy^[41].

Pegylated (PEG) filgrastim, a covalent conjugate of G-CSF and monomethoxy-polyethylene glycol, has a terminal half-life of 15-80 h, which enables less frequent administration compared to G-CSF. Given as a single 12 mg injection followed by PBSC collection, all MM patients who received PEG filgrastim successfully collected their target CD34⁺ cells/kg dose^[39]. Similarly, a multi-dose regimen of PEG filgrastim had a higher CD34⁺ cells yield on first apheresis compared to G-CSF, but no differences

in overall cell yield was observed^[46]. Its convenient dosing schedule makes it an attractive option for PBSC mobilization.

Tbo-filgrastim is a non-glycosylated recombinant methionyl human G-CSF manufactured using the bacterium strain *E. coli* K802^[47]. While not FDA approved for stem cell mobilization, retrospective data in MM patients found no difference in overall cell yield, number of apheresis sessions required for collection, nor need for rescue therapy with plerixafor^[38,48].

Myelosuppressive chemotherapy

Transient circulation of PBSC occurs during the recovery phase of chemotherapy-induced pancytopenia^[22,49,50] and is augmented by growth factor support^[22] (Table 2). This

Table 2 Growth factors following chemotherapy

Ref.	Disease	Collection strategy	n	CD34 ⁺ yield ($\times 10^6$ cell/kg): Median (range)	Failure rates n (%)
Weaver <i>et al</i> ^[91]	MM ML	G-CSF 6 μ g/kg per day	49	12 (0.1-54)	2 (4.1)
	BC	GM-CSF 250 μ g/m ² per day	49	5.4 (0.02-64)	4 (8.2)
		GM-CSF $\times 5$ d then G-CSF 6 μ g/kg per day	52	10.5 (0.4-96)	1 (1.9)
Arora <i>et al</i> ^[43]	MM	G-CSF 250 μ g/m ² per day	35	16.4 (1.1-71.7)	NR
		GM-CSF 250 μ g/m ² per day	37	12.8 (0.4-94.5)	
Tricot <i>et al</i> ^[46]	MM	PEG 6 mg q7d $\times 2$	97	NR; no difference	NR
		G-CSF 10 μ g/kg per day	140		
Fruehauf <i>et al</i> ^[92]	MM	PEG 12 mg $\times 1$	26	9.7 (4.9-40.5)	3 (11.5)
Steidl <i>et al</i> ^[93]	MM	PEG 12 mg $\times 1$	12	7.4 (4.9-38)	0
		G-CSF 8.5 μ g/kg per day	12	10.8 (5-87)	0

MM: Multiple myeloma; ML: Malignant lymphoma; BC: Breast cancer; G-CSF: Granulocyte colony stimulating factor; GM-CSF: Granulocyte macrophage colony stimulating factor; NR: Not reported; NHL: Non-hodgkin's lymphoma; PEG: Pegylated filgrastim.

Table 3 Impact of chemotherapy on cell yield and morbidity

Ref.	Collection strategy	n	CD34 ⁺ yield ($\times 10^6$ cell/kg): median (range)	Hospital days: median (range)	Infection (%)	Transfusions (%) platelet/PRBC
Desikan <i>et al</i> ^[32]	CY 6 g/m ² + G-CSF 6 μ g/kg per day	22	33.4 (NR)	No difference	18	86/86
	G-CSF 16 μ g/kg per day	22	5.8 (NR)		0	18/55
Alegre <i>et al</i> ^[51]	CY 4 g/m ² + GM-CSF	18	6.8 (1.8-34.8)	21 (16-34)	11	33.3/27.7
	G-CSF 10 μ g/kg per day	22	4.85 (2.1-10.05)	0	0	0/0
Fitoussi <i>et al</i> ^[60]	CY 7 g/m ² + HGF	74	8.6 (0.4-166)	15 (9-34)	17.6	75.7/94.6
	CY 4 g/m ² + HGF	42	13.4 (0.7-66.8)	22 (13-55)	16.7	26.2/52.4
Jantunen <i>et al</i> ^[61]	CY 4 g/m ² + G-CSF 5-10 μ g/kg per day	32	4.9 (0.8-47.4) ¹	9 (6-14)	NR	34/53
	CY 1.2-2 g/m ² + G-CSF 5 μ g/kg per day	42	5.6 (0.9-19) ¹	5 (3-12)	NR	0/28
Gojo <i>et al</i> ^[65]	CY 4.5 g/m ² + G-CSF	28	21.38 (0-106.8)	8 (4-24)	25	57/NR
	CY 4.5 g/m ² + VP-16 + G-CSF	49	22.39 (0-114.71)	7 (3-68)	53	67/NR
Hamadani <i>et al</i> ^[94]	CY 3-4 g/m ² + G-CSF	55	16.6 (2-82)	4 (1-9)	NR	21.8/34.5
	CY 1.5 g/m ² + G-CSF	68	7.5 (0-18)	3 (1-5)	NR	2.9/8.8
Hiwase <i>et al</i> ^[95]	CY 3-4 g/m ² + G-CSF	26	7.71	7 (3-22)	19	No difference
	CY 1-2.2 g/m ² + G-CSF	61	5.17	6 (3-18)	5	

¹1st apheresis session. PRBC: Packed red blood cells; CY: Cyclophosphamide; G-CSF: Granulocyte colony stimulating factor; NR: Not reported; HGF: Hematopoietic growth factor; VP-16: Etoposide.

process, chemomobilization (CM), provides not only higher cell yields than G-CSF alone, but also affords anti-myeloma activity^[32,51-54]. Cyclophosphamide (CY) 2-4 g/m², either alone or in combination with other chemotherapeutic agents, is commonly used in CM and has been a successful mobilization technique even in patients who underwent induction therapy with novel agents^[31,55-59]. The impact of increased doses of CY on PBSC yields has shown conflicting results but was consistently associated with a longer duration of neutropenia as well as the use of antibiotics and blood products^[54,60-64]. No additional impact on cell yield or objective response rate has been seen with the use of combination chemotherapy followed by growth factor^[55,65] (Table 3). Furthermore, despite the potential benefit of cyto-reduction, CM has not been associated with a better disease control or survival in MM^[32,51,52,66-68].

Chemokine receptor antagonist

The newest mobilizing agent, plerixafor, rapidly and reversibly inhibits chemokine receptor CXCR4 on HSC, thereby preventing the binding of SDF-1a to CXCR4.

Synergistic effect on PBSC mobilization is observed when plerixafor is given in combination with G-CSF^[69,70]. A phase III randomized, placebo controlled trial in MM patients compared mobilization with plerixafor + G-CSF to placebo + G-CSF. Use of plerixafor resulted in an increase in proportion of patients that were able to collect a cell yield of $\geq 6 \times 10^6$ /kg with fewer apheresis procedures compared to the G-CSF only group. Transplant outcomes were similar between groups^[71]. Plerixafor can overcome suboptimal mobilization seen with prolonged prior lenalidomide therapy and other conventional chemotherapy agents^[72,73]. Following failed attempts to mobilize, MM patients received a combination of G-CSF and plerixafor. In this population, at least 70% of patients were able to achieve a sufficient PBSC yield, without any evidence of tumor mobilization^[73,74]. Plerixafor is successful when used as the initial mobilization strategy but at an increased drug acquisition cost and in patients that presumably could have attained an appropriate cell yield with G-CSF alone^[75,76].

Risk adaptive strategies use initial mobilization with G-CSF alone and utilize plerixafor only in patients whose

Table 4 International Myeloma Working Group Consensus guidelines and recommendations on mobilization in malignant lymphoma^[20]

Strategy	Recommendations
Mobilization G-CSF alone	Limit use to patients Treated with ≤ 1 line of therapy Never exposed to melphalan Received ≤ 4 cycles of lenalidomide Use doses from 10-16 $\mu\text{g}/\text{kg}$ per day Monitor PB CD34 ⁺ count
Chemomobilization + G-CSF Plerixafor	Limit to patients who have not adequately responded to salvage therapy Suitable for all patients particularly if goals include Highest cell yield obtainable Fewer apheresis sessions
Remobilization Plerixafor	P + G-CSF or P + CM + G-CSF
Chemomobilization Bone marrow harvest	Acceptable in patients who failed cytokine mobilization Use as third-line option in patients in whom ASCT is compelling

PB CD34⁺: Peripheral blood CD34⁺ cells; P + G-CSF: Plerixafor + granulocyte colony stimulating factor; P + CM + G-CSF: Plerixafor + chemomobilization + granulocyte colony stimulating factor.

Table 5 Advantages and disadvantages of mobilization strategies

Mobilization strategy	Advantages	Disadvantages
Growth factor	Cost effective Successful mobilization in most patients Predictable schedule	No anti-myeloma effect Multiple injections and collections Potential sub-optimal yield
CM	Anti-myeloma effect Increased cell yield Fewer apheresis sessions	Cytopenias Infection risk Hospital admission Potential transfusion requirement Unpredictable count recovery
Plerixafor	Rapid kinetics Increased cell yield Fewer apheresis sessions	Higher drug cost

CM: Chemomobilization.

PB CD34⁺ count on day 4 is less than a predetermined threshold ($10 \times 10^6/\text{L}$ - $10 \times 10^9/\text{L}$). Such strategies are associated with fewer mobilization failures when compared to traditional mobilization methods and appear to be cost effective^[76-79]. Additional methods of cost reduction, namely the use of tbo-filgrastim, in combination with plerixafor has been studied. Prospective data in MM patients found similar overall cell yields without any mobilization failures^[80].

PREDICTORS OF SUBOPTIMAL MOBILIZATION

Mobilization failure is generally defined as the inability to procure 2×10^6 CD34⁺ cells/kg in 4 apheresis sessions. Despite recent advances in PBSC collection strategies, failure to obtain an adequate cell dose continues to delay and preclude auto-HCT in otherwise suitable transplant candidates. Factors associated with inadequate HSC

mobilization in MM patients include: Thrombocytopenia^[81], age > 60 years^[36,58,82], extensive treatment course^[17], prior radiotherapy, prior exposure to alkylating agents^[17,83], and prolonged use of lenalidomide^[20,21,31,84,85]. Such factors have been incorporated in consensus guidelines on stem cell mobilization (Table 4).

Lenalidomide's impact on cell yield is of particular concern due to its common use in frontline therapy^[86]. While known to cause neutropenia and thrombocytopenia, the exact mechanism of lenalidomide induced myelo-suppression is not fully known. In one study, lenalidomide was associated with a significant decrease in expression of transcription factor PU. 1, which is critical for myeloid maturation^[87]. In another study, lenalidomide-treated patients were found to have decreased BM CD34⁺ cells after six cycles of therapy^[88]. This supports the literature that identifies lenalidomide as a risk factor for suboptimal stem cell collection and suggests that transplant eligible patients receiving lenalidomide should proceed to mobilization as early as feasible.

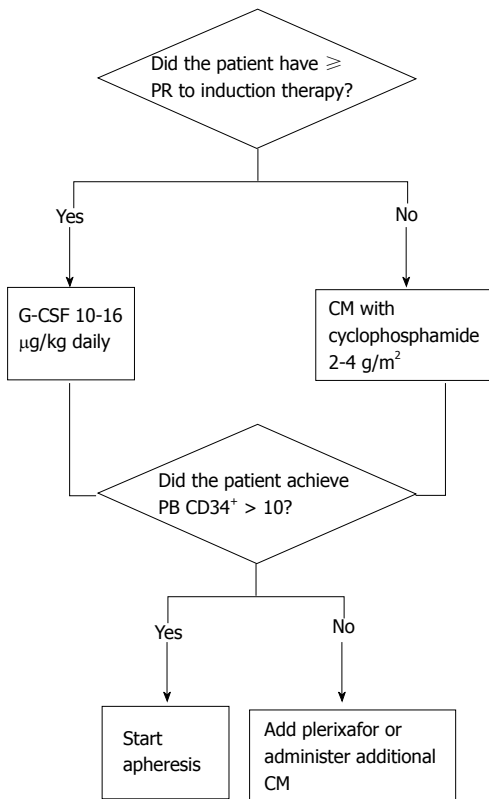


Figure 3 Mobilization strategies at authors' institution. CM: Chemomobilization; G-CSF: Granulocyte colony stimulating factor.

Despite identification of risk factors for poor mobilization, predictive algorithms have not correctly identified poor mobilizers^[89]. The best predictor of adequate CD34⁺ cell collection is the pre-collection PB CD34⁺ cell count. A strong correlation exists with PB CD34⁺ cell count and the final CD34⁺ cell collection (Figure 1). PB CD34⁺ count $\geq 20 \times 10^3$ CD34⁺ cells/mL was associated with an adequate HSC collection in 94% of patients^[16,90].

CONCLUSION

In summary, obtaining an adequate PBSC yield is essential for the successful outcome of auto-HCT in MM. Each mobilization strategy reviewed here has its own advantages and disadvantages (Table 5) and should be selected based on patient specific variables. Current practice at the authors' institution is detailed in Figure 3; however, practitioners should be cognizant of risk factors for mobilization failure and utilize appropriate algorithms to optimize stem cell collection.

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Retrospective Cohort Study

Prediction of delayed graft function using different scoring algorithms: A single-center experience

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Abstract

AIM

To compare the performance of 3 published delayed graft

function (DGF) calculators that compute the theoretical risk of DGF for each patient.

METHODS

This single-center, retrospective study included 247 consecutive kidney transplants from a deceased donor. These kidney transplantations were performed at our institution between January 2003 and December 2012. We compared the occurrence of observed DGF in our cohort with the predicted DGF according to three different published calculators. The accuracy of the calculators was evaluated by means of the c-index (receiver operating characteristic curve).

RESULTS

DGF occurred in 15.3% of the transplants under study. The c index of the Irish calculator provided an area under the curve (AUC) of 0.69 indicating an acceptable level of prediction, in contrast to the poor performance of the Jeldres nomogram (AUC = 0.54) and the Chapal nomogram (AUC = 0.51). With the Irish algorithm the predicted DGF risk and the observed DGF probabilities were close. The mean calculated DGF risk was significantly different between DGF-positive and DGF-negative subjects ($P < 0.0001$). However, at the level of the individual patient the calculated risk of DGF overlapped very widely with ranges from 10% to 51% for recipients with DGF and from 4% to 56% for those without DGF. The sensitivity, specificity and positive predictive value of a calculated DGF risk $\geq 30\%$ with the Irish nomogram were 32%, 91% and 38%.

CONCLUSION

Predictive models for DGF after kidney transplantation are performant in the population in which they were derived, but less so in external validations.

Key words: Delayed graft function; Kidney transplantation; Nomogram; Receiver operating characteristic curve; Risk calculation

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Core tip: In this single centre, retrospective study we compared the incidence of observed delayed graft function (DGF) in 247 consecutive kidney transplant recipients with the predicted risk of DGF according to 3 different nomograms. Although the Irish nomogram provided an acceptable predictive value for the global study population, this calculator did not allow to make an accurate prediction of DGF at the individual level. Our study suggests that currently available predictive models for the risk of DGF after kidney transplantation are predictive in the population in which they were derived, but they lose their predictive value in external validations.

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INTRODUCTION

Delayed graft function (DGF) is classically defined as the need for at least one postoperative dialysis session during the first week after transplantation^[1,2]. This definition has some limitations since the postoperative requirement of dialysis is not standardized and the decision to dialyze is subjective. For this and other reasons, the frequency of DGF varies worldwide between 10% and 40% for deceased donor kidney transplants^[1,3]. DGF leads to prolonged hospitalization, higher cost of transplantation, and increased complexity of management of immuno-suppressive drugs^[4-6]. DGF is associated with an increased risk of acute rejection and may negatively impact long-term allograft function and outcome^[7,8].

There are currently neither clinical practice guidelines nor an approved therapy to prevent DGF. In addition, the use of "extended criteria donors" (ECD) and kidneys from donors after cardiac death (DCD), which are associated with a higher incidence of DGF, is rising. The ability to predict DGF at the time of the transplant offer might help in clinical decisions making, such as declining the offer, selecting a recipient who would have a lower DGF risk, or modifying the transplantation strategy. This may include efforts to shorten the cold ischemia time (CIT), or delay the initiation of calcineurin inhibitors (CNIs) under the cover of induction therapy with anti-lymphocyte antibodies, or even to machine-perfuse the kidney.

Recently several DGF-scoring systems have been developed. In 2003, Irish *et al*^[6], using a combination of 16 donor- and recipient-related risk factors known at the time of transplantation, developed a nomogram to predict/quantify the risk of DGF after renal transplantation. In 2010 they refined their previously published model using a more recent data set and adding two risk factors (in total 18) to the analysis (Table 1)^[9]. This predictive model has an area under the receiver operating characteristic curve (ROC AUC) of 0.70, which indicates a good degree of discrimination^[9]. In 2009, Jeldres *et al*^[10] developed a simpler but equally accurate scoring system on 532 patients (6 variables, AUC = 0.74) (Table 1). More recently Chapal *et al*^[11] proposed a predictive score that could be calculated by computing only 5 variables with a ROC AUC of 0.73 (Table 1).

The main aim of our study was to conduct a single-center retrospective analysis of a cohort of 247 adult patients to evaluate the performance of available nomograms to predict DGF in our patients, *i.e.*, in a different population than the one they have been tested in. We also studied separately recipients of standard criteria,

Table 1 Comparison of variables used in different scoring systems

	DGF risk calculator (Irish <i>et al</i> ^[9])	DGFS scoring system (Chapal <i>et al</i> ^[11])	Jeldres scoring system (Jeldres <i>et al</i> ^[10])
Recipient variables			
Recipient BMI	+	+	-
Recipient age	+	-	+
No. of HLA mismatches	+	-	+
Peak PRA (%)	+	-	+
Recipient race	+	-	-
Recipient gender	+	-	-
Duration of dialysis	+	-	-
History of diabetes mellitus	+	-	-
Previous transplantation or blood transfusion	+	-	-
Single or multiple organ transplant	+	-	-
Recipient weight	-	-	+
Donor variables			
Donor age	+	+	+
Duration of CIT	+	+	+
Terminal serum creatinine	+	+	-
Donor weight	+	-	-
Primary cause of death	+	-	-
History of hypertension	+	-	-
Duration of WIT	+	-	-
Type of the donor (living, DCD)	+	-	-
Type of induction therapy	-	+	-

PRA: Panel-reactive antibody; WIT: Warm ischemia time; CIT: Cold ischemia time; DCD: Donation after cardiac death; DGF: Delayed graft function.

extended criteria and donation after cardiac death donors.

MATERIALS AND METHODS

Patient characteristics

From January 1st 2003 to December 31st 2012, 349 renal transplantations were performed at the Antwerp University Hospital. Data were collected from our prospective institutional database and the database of Eurotransplant International Foundation. We excluded 27 pediatric transplants (aged < 18), 16 combined solid organ transplantations in adults (13 pancreases and 3 hearts), 31 transplantations performed with living donors (10.1%), 2 pre-emptive transplantations and 15 machine perfused kidneys. Moreover, we excluded 5 patients because of missing data for CIT. Thus, a total of 253 kidney transplantations from a deceased donor (87% first and 13% re-grafts), performed on 243 patients were considered for study. Six out of those 253 grafts (2%) were lost due to primary non function (PNF). These patients were excluded from further analysis and the final data set comprised 247 transplantations. Recipient and donor characteristics at the time of transplantation are summarized in Tables 2 and 3.

Definition of DGF, PNF and ECD

DGF was defined as the requirement of at least one dialysis within the first 7 d post-transplantation. The duration of DGF was defined as the number of days between the transplantation and the day of the last

dialysis. PNF was defined as the absence of allograft function starting immediately after transplantation, and requiring maintenance dialysis. An ECD was defined as: A donor aged ≥ 60 years, or a donor aged 50-59 years with at least 2 of the following conditions: History of hypertension, terminal serum creatinine level greater than 1.5 mg/dL, or death resulting from a cerebrovascular accident/stroke (CVA).

Post-transplant immunosuppressive therapy

One hundred and sixty-one patients (63.6%) were given an induction with an inhibitor of the IL2-receptor (basiliximab or daclizumab). Ninety-two patients (36.4%) were induced with antithymocyte globulin (ATG). According to our induction immunosuppression protocols ATG was given to immunized patients (peak PRA > 50%), patients of North-African origin, patients with a history of acute rejection during the first year after previous transplantation or in the case of kidney transplantation with ECD or DCD donor kidneys. Most patients ($n = 244$, 96.4%) received a CNI as initial therapy in addition to the treatment with corticosteroids and mycophenolate mofetil. Cyclosporin A was initiated at a starting dose of 2×4 mg/kg at post-transplant day 1. Only 7 patients (2.8%) were given mTOR-inhibitors. Two remaining patients (0.8%) [Eurotransplant Senior Program (ESP)] did not receive either medication but only ATG, MMF and prednisolone.

Data collection and DGF risk assessment

Risk factors for DGF included donor^[12-15] and recipient factors known before and at the time of the transplantation

Table 2 Recipient characteristics at the time of transplantation

Age (yr)	50.2 ± 11.9 ²
Origin (%)	
Blacks	4.5
Caucasians	95.5
Gender (%)	
Male	61.9
History of diabetes mellitus (%)	
Yes	16.6
Body mass index (kg/m ²)	25.1 ± 3.8 ²
Pretransplant transfusions (%)	
Yes	38.1
No	56.7
Unknown	5.3
Duration of the pre-transplant renal replacement therapy (mo)	26.7 (16.4-43.5) ¹
Peak panel-reactive antibodies (%)	88.5
≤ 5%	9.5
5%-80%	2
≥ 80%	
Proportion of kidney re-graft (%)	12.6
Total HLA mismatches	3 (2-3) ¹

¹Median with P25-75; ²Mean ± standard deviation (SD).

and were required to calculate the risk of DGF with the DGF risk calculator^[9] (www.transplantcalculator.com/DGF), the Jeldres scoring system (Jeldres *et al.*^[10]) and the DGFS scoring system^[11]. Recipient variables included: Age, gender, race, body mass index (BMI), history of diabetes mellitus, previous transplantation, pretransplant blood transfusion, duration of renal replacement therapy (RRT), the percentage of serum panel-reactive antibodies (peak PRA), and the number of HLA mismatches. Donor variables included: Age, gender, weight, donor type [standard criteria donor (SCD), ECD, DCD], primary cause of death, history of hypertension, duration of cold (CIT) and second warm ischemia time (WIT), and the terminal serum creatinin (mg/dL).

Statistical analysis

The statistical methods were performed and reviewed by Kristien Wouters (Department of Medical Statistics, Antwerp University Hospital, B-2650 Edegem, Belgium) and by Erik Fransen (StatUa Center for Statistics, University of Antwerp, B-2610 Wilrijk, Belgium).

Normality was tested with the Shapiro-Wilk and the Q-Q plot test. Normally distributed data are represented as mean and standard deviation; non-normally distributed data as median with P25 and P75. Categorical data are presented as numbers and percentages. Comparison of predicted DGF probability between DGF positive and negative patients was done by means of the Mann-Whitney *U* test. Receiver operating characteristic (ROC) curves were generated to evaluate the performance of explanatory scoring systems in predicting outcomes. The c-statistic (or AUC = area under ROC curve) was used as a measure of the predictive performance of the studied scoring systems. Additionally, the performance of the 3 nomograms was evaluated using a Hosmer-Lemeshow goodness-of-fit test. All data were analyzed using IBM

Table 3 Donor characteristics at the time of transplantation

Age (yr)	45.1 ± 14.1 ²
Weight (kg)	76.2 ± 16.4 ²
History of hypertension (%)	
Yes	23.1
No	74.5
Unknown	2.4
Terminal serum creatinine (mg/dL)	0.78 (0.61-1.00) ¹
Donor type (%)	
Standard criteria donor	68.8
Extended criteria donor	17
Donation after cardiac death donor	14.2
Primary cause of death (%)	
Cerebrovascular accident/stroke	27.1
Anoxia	8.1
Other	64.8
Cold ischemia time (h)	14 ± 4.7 ²
Second warm ischemia time (min)	32.8 ± 7.9 ²

¹Median with P25-75; ²Mean ± standard deviation (SD).

SPSS statistics (version 21). Statistical significance was predefined as a *P*-value < 0.05. Goodness-of-fit was set at *P* > 0.05 for the Hosmer-Lemeshow test.

RESULTS

DGF occurred in 38 of the 247 transplants under study (15.3%). The mean duration of DGF was 11.3 ± 15.1 d (range 1-71 d). Graft survival at one year was comparable in patients with or without DGF (94.6% vs 93.3% respectively, *P* = ns). However, graft function was significantly inferior in patients with DGF both at 30 d (creatinine clearance according to MDRD formula 31 ± 16 mL/min vs 46 ± 17 mL/min, *P* = 0.001) and at 1 year (42 ± 14 mL/min vs 52 ± 17 mL/min, *P* < 0.001).

Analysis according to the algorithm of Irish *et al.*^[9]

At the population level, the average DGF risk calculated with the DGF risk calculator was 18.5%, which was close to the observed data (DGF rate: 15.3%). The AUC was 0.69 (Figure 1). Figure 2A illustrates the relatively good calibration of the Irish model. The predicted DGF risk and the observed DGF probabilities were close (*P* = 0.74, Hosmer-Lemeshow statistic). The mean calculated DGF risk was significantly different (*P* < 0.0001) between DGF-positive and DGF-negative subjects (Figure 3). However, at the level of the individual patient the calculated risk of DGF overlapped very widely (Figure 3). Indeed, it ranged from 10% to 51% for recipients with DGF and from 4% to 56% for those without DGF. The sensitivity, specificity and positive predictive value of a calculated DGF risk ≥ 30% were 32%, 91% and 38% respectively.

Analysis according to the algorithm of Jeldres *et al.*^[10]

At the population level, the average DGF risk calculated with Jeldres nomogram was 27.9%, which is almost the double of the observed DGF rate (15.3%). The AUC of the ROC curve was poor at 0.54 (Figure 1). The

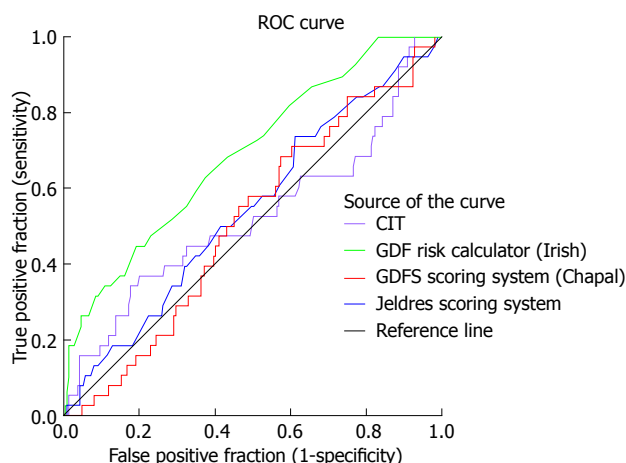


Figure 1 Receiver operating characteristic curves to evaluate the prognostic capacity of cold ischemia time, the delayed graft function risk calculator, the Jeldres scoring system^[10] and the DGFS scoring system^[11] to predict delayed graft function. The cold ischemia time (purple-line): Area under ROC curve (AUC) = 0.52. The DGF risk calculator (green-line) proposed by Irish *et al*^[9]: AUC = 0.69. The scoring system (blue-line) proposed by Jeldres *et al*^[10]: AUC = 0.54. The DGFS scoring system (red-line) proposed by Chapal *et al*^[11]: AUC = 0.51. ROC: Receiver operating characteristic; CIT: Cold ischemia time; DGF: Delayed graft function.

Hosmer-Lemeshow “goodness-of-fit” test demonstrated a significant difference ($P < 0.05$) between the predicted DGF risk and the observed DGF, which indicates that the DGF risk was not well estimated by the Jeldres scoring system (Figure 2B). The calculated risk of DGF showed a wide range of values from 5%-82% in the DGF-group and 3%-83% in the non- DGF-group with a very large overlap between both groups (Figure 4). The sensitivity, specificity and positive predictive value of a calculated DGF risk $\geq 30\%$ was 44.7%, 61.7% and 17.5% respectively.

Analysis according to the algorithm of Chapal *et al*^[11]

The average DGFS value was -0.48 [$(-0.46) \pm 0.76$; 95%CI: $(-0.43) - (-0.71)$] in the DGF positive group and $(-0.48) \pm 0.89$; 95%CI: $(-0.46) - (-0.60)$ in the DGF negative group] (Figure 5A), indicating the inability of the Chapal score to predict DGF in our population. The sensitivity, specificity and negative predictive value of a DGFS value $\leq (-0.5)$ were 45.6%, 70.3% and 85.8% respectively. Only 3 patients (1.2%) had a DGFS score ≥ 1.2 , which should in theory point to a high risk of DGF. None of these 3 patients developed DGF (sensitivity and positive predictive value for DGFS score ≥ 1.2 was 0).

The average DGF risk calculated with the DGFS nomogram was 20%. The ROC curve analysis showed a c-index of 0.51 (Figure 1), indicating the absence of any predictive value. There was no difference between the median calculated DGF risk in the DGF-positive and the DGF-negative subjects (Figure 5B). The calibration plot of this model (Figure 2C) showed a significant difference ($P = 0.02$) between the predicted DGF risk and the observed DGF, which indicates that the DGF risk was not well calibrated by the Chapal nomogram. The

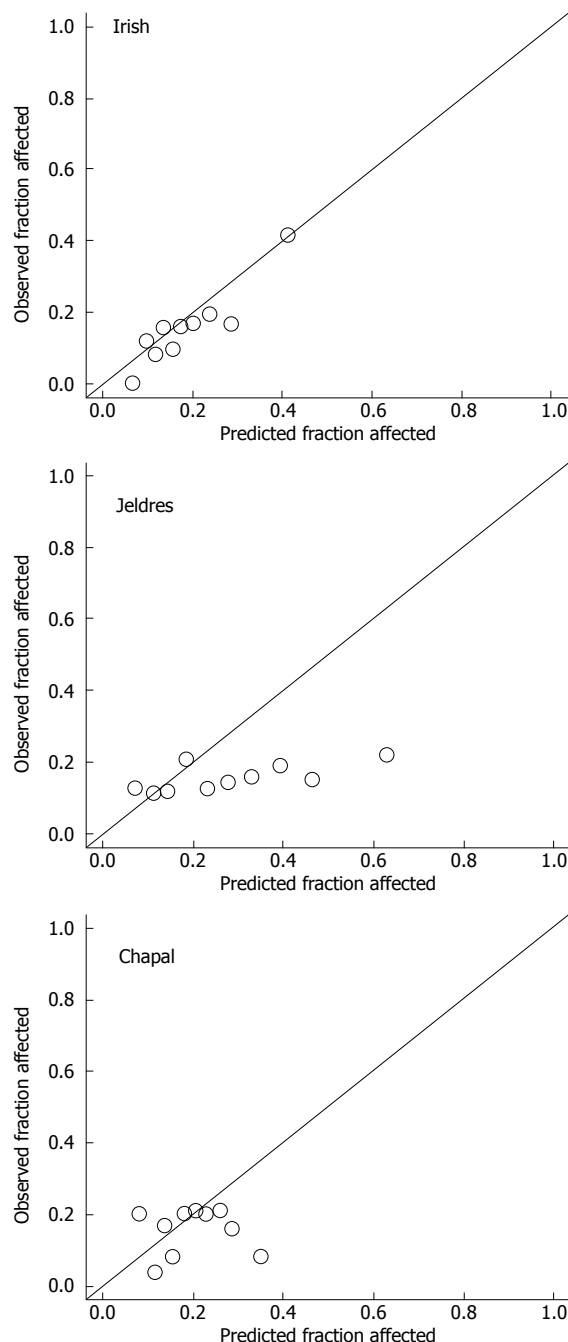


Figure 2 Calibration plot of: The delayed graft function risk calculator (Irish *et al*^[9]), the Jeldres scoring system^[10] and the DGFS scoring system (Chapal *et al*^[11]) to predict delayed graft function. Patients were divided into 10 subgroups (deciles of increased DGF risk), based upon the risk prediction. Each figure plots the mean predicted probability (X-axis) of DGF against the observed prevalence of DGF (Y-axis) (Hosmer-Lemeshow). The P -values were 0.74 for the Irish score, < 0.05 for the Jeldres score and 0.02 for the Chapal score. DGF: Delayed graft function.

sensitivity, specificity and positive predictive value of a calculated DGF risk $\geq 30\%$ were 5.2%, 88% and 8% respectively.

Analysis in the subgroups with a higher risk of DGF

Next, we studied how well the three nomograms can predict DGF in subgroups of patients considered to be at increased risk of DGF such as ECD and DCD donors

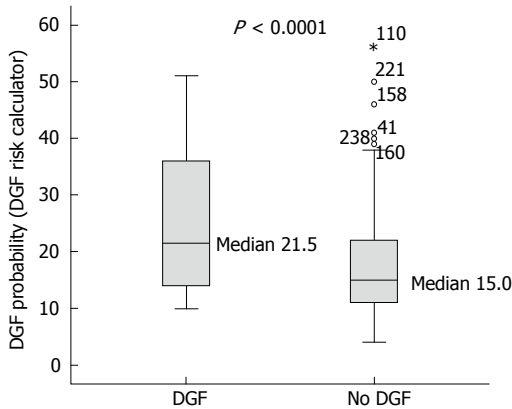


Figure 3 Correlation between the predicted delayed graft function probability according to the delayed graft function risk calculator (Irish *et al*^[9]) and the presence or absence of delayed graft function. DGF: Delayed graft function.

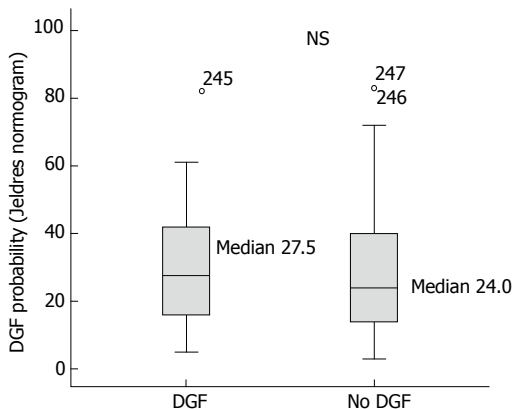


Figure 4 Correlation between the predicted delayed graft function probability according to the Jeldres scoring system (Jeldres *et al*^[10]) and the presence or absence of delayed graft function. DGF: Delayed graft function.

(Table 4). The results presented in Table 4 suggest an acceptable agreement between the observed prevalence of DGF and the Irish DGF score for DCD donors, but not for ECD donors. The DGFS scoring system and the Jeldres scoring system^[10] could not predict DGF in these high-risk groups (Table 4).

DISCUSSION

The first finding from our study is that our mean DGF rate was in the low range (15%), with a stepwise increase according to the risk categories (SCD, ECD, DCD donors). Next, we found that, at a population level, the observed DGF rate and the median calculated DGF risk according to the Irish calculator (16%) were similar. In our study the AUC calculated according to the Irish calculator was 0.69 which is similar to the results obtained in the 2010 Irish model (AUC of 0.70) and indicates an acceptable degree of discrimination. Along this line, the Hosmer-Lemeshow “goodness-of-fit” test demonstrated that the DGF risk was well calibrated by the DGF risk calculator. With regards to the ECD and DCD high-risk groups, there was a good agreement for

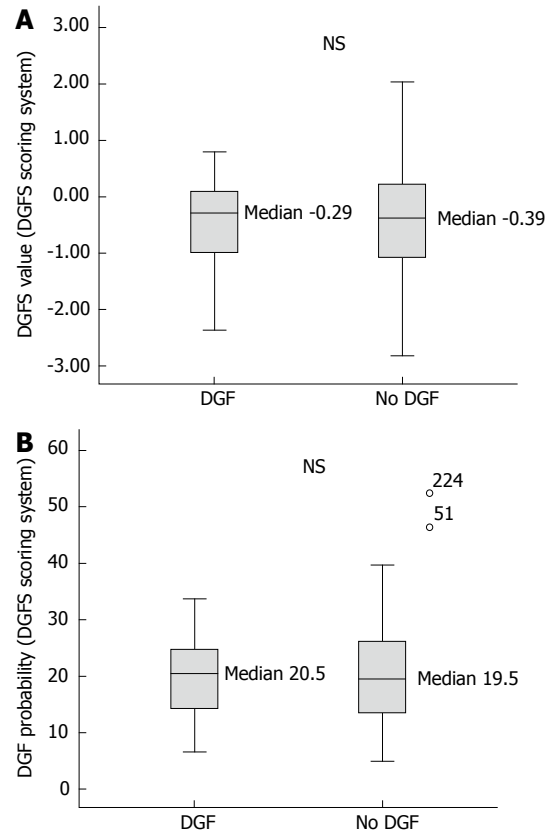


Figure 5 Correlation between the DGFS value (A: Y-axis) and the predicted delayed graft function probability according to the DGFS scoring system (Chapal *et al*^[11]) (B: Y-axis) and the presence or absence of delayed graft function (A and B: X-axis). DGF: Delayed graft function.

DCD but not for ECD. This could be due to the smaller number of patients tested with these conditions in our center. While it appears that the DGF risk calculator can relatively well predict the percentage of DGF in our global study group, it is obvious that we cannot use this tool to take clinical decisions for individual patients. Indeed, as seen in Figure 3, because of the large overlap in DGF risk prediction between patients who developed DGF and those who did not, a high- or low-risk score did not correspond with the presence or absence of DGF. The specificity, sensitivity and positive predictive value of the DGF-risk calculator are too low to help with clinical-decision making regarding the immunosuppressive strategy. This nomogram has been previously tested in Australian^[8], North American^[16] and European^[17] populations, but yielded conflicting results. In the Australian cohort from Kaiser *et al*^[8] the nomogram was applied to 598 deceased donor renal transplantations, and showed a slightly better AUC value of 0.76 with a sensitivity of 74% and a specificity of 71%. Of note, however, no data are given about the overlap between the DGF and no DGF patients in this series, and it is thus difficult to evaluate its predictive value at individual patient level. Moore *et al*^[17] evaluated the nomogram of Irish on 210 United Kingdom patients and showed a similar predictive value with an AUC of 0.71 with a high specificity (95%) but a very poor

Table 4 Observed prevalence *vs* predicted probability of delayed graft function in the overall population and by risk group

Kidney graft according to donor type	Observed prevalence of DGF (%)	Probability of DGF predicted by the DGF risk calculator (%) (Irish <i>et al</i> ^[9])	Probability of DGF predicted by the DGF scoring system (%) (Chapal <i>et al</i> ^[11])	Probability of DGF predicted by the Jeldres scoring system (%) (Jeldres <i>et al</i> ^[10])
Overall population (<i>n</i> = 247)	15.3	16 ¹ 12-24 ² 0.69 ³	19.7 ¹ 13.6-26 ² 0.51 ³	25 ¹ 14-40 ² 0.54 ³
Standard criteria donor (<i>n</i> = 170)	11.8	14 ¹ 10-20 ² 0.73 ³	20.1 ¹ 14.5-26.4 ² 0.60 ³	21 ¹ 13.7-34.2 ² 0.54 ³
Extended criteria donor (<i>n</i> = 42)	19	19.5 ¹ 14-25 ² 0.39 ³	21.2 ¹ 14.4-27.6 ² 0.34 ³	41.5 ¹ 25.7-60 ² 0.38 ³
Donation after cardiac death (<i>n</i> = 35)	28.6	30 ¹ 18-38 ² 0.65 ³	11.8 ¹ 9.1-20.4 ² 0.58 ³	21 ¹ 8-39 ² 0.64 ³

¹Median; ²P25-P75; ³AUC of the ROC curve. DGF: Delayed graft function.

sensitivity (25%) at a score > 150. They concluded that the utility of the nomogram score in predicting DGF was moderate at best. Grossberg *et al*^[16] showed a poor association between the Irish nomogram and DGF (the average DGF risk in DGF-positive patients was 0.45 ± 0.14 vs 0.40 ± 0.14 in DGF-negatives, $P = 0.07$) in a US population of 169 patients, but they did not report a c-index.

In 2012, Rodrigo *et al*^[18], used the web-based calculator to predict DGF on 342 European renal transplants. Similar to the Irish group^[9] they found an AUC of 0.71. The reported specificity and sensitivity of a calculated DGF risk $\geq 30\%$ were 75.8% and 51.8% respectively. They concluded, like us, that there was overlap in DGF risk prediction, which limited the utility of the score for individual patients. Finally, a large number of variables are needed to calculate the Irish DGF risk score, which limits its usefulness in daily clinical practice.

For this particular reason, two other independent and easier scoring systems were developed^[10,11]. Jeldres *et al*^[10] developed a more user-friendly nomogram based on the analysis of 6 risk factors. The c-statistic for assessing the predictive ability of Jeldres score for DGF (internal validation) was very similar to the Irish scoring system (AUC of 0.74). However, Chapal *et al*^[11] tried to validate Jeldres score on their patients and showed an inferior predictive capacity of this scoring system to predict DGF (AUC = 0.61). The ROC curve analysis based on our population showed that the predictive utility of the Jeldres scoring system was poor, with a c-index of 0.54. This poor predictive value was confirmed by the Hosmer-Lemeshow "goodness-of-fit" test that showed a bad calibration of this model. The median calculated DGF risk in the DGF-positive group did not differ significantly from the DGF-negative group and there was a large overlap between both groups. Jeldres *et al*^[10] proposed no cut-off to classify patients according to their DGF risk in their original study.

In our study the predictive capacity of the DGFS scoring system from Chapal was poor with an AUC of

0.51. In our population the negative predictive value of the DGFS score was 0.86 which implies that with the DGFS scoring system we can fairly well recognize the patients at a low risk of DGF. In contrast, the threshold for high risk of DGF was clinically useless in our study (none of the patients with DGFS score ≥ 1.2 actually developed DGF). The failure of the DGFS scoring system in the prediction of DGF in our study may be explained by a lower incidence of DGF in our population (15.3% in our study vs 25.5% in the study of Chapal *et al*^[11]). This difference is the consequence of shorter CIT [14 h (range 2.8 to 29.9 h) vs 19.2 h (range 6.0 to 58.6 h)], use of kidneys from younger donors (45.1 years vs 51.9 years) and lower terminal donor serum creatinine (69 $\mu\text{mol/L}$ vs 91 $\mu\text{mol/L}$) in respectively our study population and in the study by Chapal^[11]. According to these data our center seems to be more stringent in the selection of donors. This could also explain why the algorithm proposed by Chapal *et al*^[11] fails to predict adequately DGF in our population.

There are some limitations to our study. First, the need to dialyse within the first week after the transplantation is an endpoint that could be influenced by several clinical factors (such as for instance heart failure, hyperkalemia...). This can lead to obvious mistakes in the validation of different scoring systems. Second, the sample size in our study is relatively small, particularly when compared to large-population-based transplant registers. Finally, the composition of our study population differs from the initial studies [e.g., 4.5% blacks in our population vs 30.1% blacks in the study of Irish; relatively short CIT in our study (14 ± 4.7 h vs 19.2 ± 7 h in the study of Chapal or 17.8 ± 7.8 h in the study of Irish)]. And finally, according to our induction immunosuppression protocols ATG was de facto given to the patients at increased risk for DGF. The delayed introduction of CNIs could have attenuated the incidence of DGF in our population at risk. Another issue not captured by any scoring system is the policy of peri-operative volemia control, which has been shown to play an important role in the incidence of DGF (Mikhalski

et al^[41]).

In summary, our study suggests that currently available predictive models for the risk of DGF after kidney transplantation are predictive in the population in which they were derived, but they lose their predictive value in external validations. This is not surprising, as none of these scores has been previously rigorously validated in external population of patients. Along this line, there were large variations between centers regarding demographic values (donor age, CIT, proportion of ECD/DCD, *etc.*) explaining why external validation like the one we tried, failed. This means that we still need better predictive tools for the kidney allocation to individual patients, especially those patients who are at high risk of DGF. Currently we are unable to further improve the outcome of a single patient by altering our management on the basis of available scores for the risk of DGF.

COMMENTS

Background

Delayed graft function (DGF) occurs in 10% to 40% of deceased donor kidney transplantations, and leads to prolonged hospitalization, higher costs of transplantation, and increased complexity of management of immunosuppressive drugs. The ability to predict DGF at the time of the transplant offer might help in clinical decision making, such as declining the offer, selecting a recipient who would have a lower DGF risk, or modifying the transplantation strategy. Three predictive scoring systems for DGF were previously developed and published (Irish *et al*, Jeldres *et al* and Chapal *et al*). However, since these scores were not validated in an external study population, we decided to analyse the performance of these three scoring systems in a single centre cohort of 247 consecutive kidney transplant recipients at our institution between 2003 and 2013.

Research frontiers

Three different scoring systems for the prediction of DGF have been developed and validated in the past in respectively well-defined study populations, specific for each study. However, these scoring systems were never validated in an external study population (*i.e.*, different from the initial study population). To explore the validity of these three predictive models, we retrospectively analysed their performance in a cohort of 247 consecutive kidney transplant recipients at our institution.

Innovations and breakthroughs

DGF occurred in 15% of this study population. Only the Irish calculator provided an acceptable level of prediction for DGF with an AUC of the ROC curve of 0.69. However, at the level of the individual patient the calculated risk of DGF overlapped very widely, and therefore this predictive score was not useful in clinical decision making in our study population.

Applications

Based on the reported literature and on our data, we conclude that predictive models for DGF are performant in the population in which they were derived, but these models require additional validation in an external study population.

Terminology

DGF: Delayed graft function; AUC: Area under the curve; ROC: Receiver operator curve; C index: The index of concordance is a "global" index for validating the predictive ability of an algorithm (*e.g.*, for the occurrence of DGF); Nomogram: Is a prediction tool based on information from large numbers of patients. Predictive data are put in a mathematical model that enables to calculate a hypothetical outcome measure.

Peer-review

It is very well-conducted study with some interesting findings, mostly pointed

out that we still cannot predict with accuracy the development of DGF. The study design and method, and statistical analysis were all well-thought and accurately followed throughout the paper.

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Observational Study

Graft loss among renal-transplant recipients with early reduction of immunosuppression for BK viremia

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Abstract

AIM

To review the incidence of graft loss and acute rejection among renal transplant recipients with early reduction of immunosuppression for BK viremia.

METHODS

We performed a retrospective analysis of consecutive *de-novo* kidney-only transplants from January 2009 to December 2012 to evaluate the incidence of Polyoma-virus associated nephropathy (PyVAN). Recipient plasma was screened for BKV DNA *via* quantitative polymerase chain reaction (PCR) at months 1, 3, 6, 9 and 12 post-transplant and on worsening graft function.

Immunosuppression was reduced at ≥ 3 -log copies/mL. Those with viremia of ≥ 4 -log copies/mL (presumptive PyVAN) underwent renal transplant biopsy. Presumptive PyVAN (PP) and definitive PyVAN (DP; biopsy-proven) were treated by immunosuppression reduction (IR) only.

RESULTS

Among 319 kidney transplant recipients, the median age was 53 years (range 19-83), 65.8% were male, and 58.9% were white. Biopsy-proven acute rejection was found in 18.5% within 0-168 wk. Death-censored graft loss occurred in 5.3% ($n = 17$) and graft loss attributable to PyVAN was 0.6% ($n = 2$). Forty-seven patients were diagnosed with PP (14.7%) and 18 (5.6%) with DP. Graft loss among participants with PyVAN (8.5%) and those without (4.8%) was not significantly different. Deceased donor kidney transplantation (OR = 2.3, 95%CI = 1.1-4.6) and AR (OR = 2.3, 95%CI = 1.2-4.7) were associated with PyVAN in the multivariate analysis. BK viremia between 3 and 4-log copies/mL occurred in 27 patients, all of whom underwent IR. Of these, 16 (59%) never developed PyVAN while 11 (41%) developed PyVAN (4 DP, 7 PP) within a range of 11-39 wk.

CONCLUSION

Instituting an early reduction of immunosuppression, in the absence of adjunctive antivirals, is effective at preventing PyVAN and may be associated with a lower incidence of graft-loss without a reciprocal increase in the incidence of acute rejection.

Key words: BK virus; Renal transplant; Screening; PyVAN; Prevention; Graft loss

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Core tip: The authors describe results of a retrospective study of 319 renal transplant recipients who underwent reduction of immunosuppression for BK viremia at a BK viral of ≥ 3 -log copies/mL. Instituting early reduction of immunosuppression in the absence of adjunctive antivirals was effective in reducing the incidence of graft loss due to Polyoma-virus associated nephropathy (PyVAN) without a reciprocal increase in acute rejection. Our study also emphasizes that efforts to implement universal BK virus polymerase chain reaction assay standards recently developed by the World Health Organization are key in establishing a preventative strategy for PyVAN that is widely applicable and highly effective.

Azar MM, Assi R, Valika AK, Banach DB, Hall IE, Landry ML, Malinis MF. Graft loss among renal-transplant recipients with early reduction of immunosuppression for BK viremia. *World J Transplant* 2017; 7(5): 269-275 Available from: URL: <http://www.wjgnet.com/2220-3230/full/v7/i5/269.htm> DOI: <http://dx.doi.org/10.5500/wjt.v7.i5.269>

INTRODUCTION

BK virus (BKV) is a polyomavirus that causes widespread sub-clinical infection at a young age and subsequently establishes long-term latency in cells of the renal and urinary systems. In recipients of renal allograft transplants and allogeneic hematopoietic stem cell transplants, high-level BKV replication may lead to overt clinical disease. BK-polyoma virus associated nephropathy (PyVAN) is a major complication of kidney transplantation, occurring in 1%-10% of renal transplant recipients^[1,2]. PyVAN is directly associated with graft failure^[3,4] due to progressive interstitial nephritis and indirectly linked to allograft rejection due to immunosuppression reduction (IR), which is the cornerstone of PyVAN treatment^[5]. Guidelines currently recommend prospective screening for BKV reactivation post-transplantation, by using urine cytology to detect decoy cells or testing for high-level BK viremia and/or viremia. In the event of a sustained BK viremia of ≥ 4 -log copies/mL for more than 3 wk, a renal biopsy is recommended to confirm the diagnosis of PyVAN by demonstrating polyomavirus cytopathic changes with confirmation by immunohistochemical staining^[6]. In addition, a prompt reduction of immunosuppression is critical in an attempt to abrogate the full-fledged manifestations of the disease. Although agents with anti-BK activity such as leflunomide^[7], cidofovir^[8] and quinolones^[9] have been used^[10], randomized controlled trials proving their efficacy are lacking.

The positive predictive value of BK viremia at a cut-off of 7×10^3 copies/mL (approximately 4 log copies/mL) has been estimated at 50% to 60% for detecting proven PyVAN within 2 to 6 wk but rises to 90% when a threshold of 6-log copies/mL is implemented^[1,11,12]. A lower threshold of 3-log copies/mL may increase the sensitivity, leading to the identification of more cases, and earlier in the natural course when intervention may be more effective and graft loss more likely to be averted. In this paper, we aim to assess the incidence of PyVAN and graft loss in a single transplant center while implementing a reduction of immunosuppression at BKV loads of ≥ 3 -log BKV copies/mL.

MATERIALS AND METHODS

We performed a retrospective analysis of consecutive de-novo kidney transplants at Yale-New Haven Hospital (YNHH), who underwent screening for PyVAN screening and prevention, from January 2009 to December 2012. The Yale University Institutional Review Board approved this study and all procedures conducted were in accordance with the Helsinki Declaration of 1975. Individuals included in the study were above the age of 18 years and underwent primary kidney-only transplant. Medical records were reviewed for data on demographics,

comorbidities, and transplant parameters including type of transplant (deceased or living donor), CMV donor and recipient serostatus, induction and maintenance immunosuppression, presence of delayed graft function (DGF), biopsy-proven acute rejection (AR), graft loss and its etiology, last follow-up visit, deaths, BK viral load (copies/mL) and biopsy-proven PyVAN. Graft loss was censored for episodes of death with a functioning graft.

Presumptive PyVAN (PP) was defined as sustained BK viremia ≥ 4 -log copies/mL while definitive PyVAN (DP) required cytopathic changes on renal biopsy that were confirmed by positive BKV immunohistochemistry^[6]. Renal allograft rejection was graded in accordance with the BANFF working classification of renal allograft pathology^[13]. DGF was defined as acute renal failure requiring dialysis within 7 d of transplantation. Graft failure was defined as chronic allograft nephropathy leading to the resumption of chronic renal replacement therapy. Primary outcomes included both presumptive and definitive PyVAN while the secondary outcomes were graft survival and acute rejection.

The YNHH kidney transplant program has been active since 1967 and performs approximately 100 kidney transplantations annually. The standard maintenance immunosuppressive regimen consists of tacrolimus, mycophenolate mofetil and low dose prednisone (5-10 mg daily). The target tacrolimus trough level for the first 30 d post-transplant was 8-10 ng/mL and 5-7 ng/mL thereafter. As part of the institutional protocol for PyVAN screening and prevention, transplant recipient plasma is screened for BKV DNA *via* quantitative PCR. For the first two years of the study, an NIH-developed, real-time BKV PCR assay targeting the viral T antigen gene was used^[14]. Due to concerns about potential under-quantitation of some BKV subtypes, a multiplex real-time PCR assay developed at the University of Washington (UW) that targets both VP1 and T genes using two primer sets and three probes was implemented in December 2010^[15].

Per protocol, a serum BKV DNA viral load (VL) is obtained at months 1, 3, 6, 9 and 12 post-transplant and in case of worsening graft function. A BKV DNA VL between 3 and 3.99 log copies/mL prompted a 50% dose reduction of mycophenolate mofetil, a reduced target tacrolimus trough level of 5 ng/mL and monthly plasma BKVL until negative. Additionally, mycophenolate mofetil was discontinued and a renal biopsy was with immunohistochemical staining was performed if the serum BKV VL was above ≥ 4 -log copies/mL PP and DP were treated by reduction of immunosuppression, without adjunctive anti-viral treatment.

Statistical analysis

Statistical analysis was performed using SPSS software, version 16.0.0.0. In univariate analyses, χ^2 and Fisher's exact test (when appropriate) were used to evaluate categorical variables and Mann-Whitney *U* test was used for continuous variables. Predictors of PyVAN were identified using a multivariate logistic regression model. Only

variables with a *P*-value < 0.10 on univariate analysis were entered into a stepwise multivariate logistic regression model to identify factors independently associated with Presumptive PyVAN. All tests were double-tailed, with an assumed type 1 error risk a equal to 5%. Kaplan-Meier survival curves were plotted using GraphPad Prism version 6.03 (GraphPad Software, San Diego, CA, United States).

RESULTS

A total of 330 primary kidney transplant recipients were identified and were followed for a median time of 42 ± 14.7 mo. BK screening data on 11 patients was unavailable and thus they were excluded, leaving 319 patients available for analysis. The median age was 53 years (range 19-83), 65.8% were male, 58.9% were white, and 27.0% had diabetes mellitus. A CMV D+/R-serostatus was present in 18.2% of transplants and 54.5% of recipients underwent a deceased-donor kidney transplantation (DDKT). Induction immunosuppressive therapy consisted of basiliximab (44.8%), anti-thymocyte globulin (37.0%) or daclizumab (17.6%). Maintenance immunosuppressive therapy included both a calcineurin inhibitor and mycophenolate mofetil in 95% of cases and 95% received steroids. Biopsy-proven rejection was found in 18.5% ($n = 59$) of transplant recipients within 0-168 wk. Graft loss occurred in 5.3% ($n = 17$) and PyVAN-associated graft loss occurred in 0.6% ($n = 2$). Causes of graft loss included: AR ($n = 7$), antibody-mediated chronic rejection ($n = 2$), PyVAN ($n = 2$), CMV nephropathy ($n = 1$), hypoplastic kidney disease ($n = 1$), ureteral obstruction ($n = 1$), renal graft vein thrombosis ($n = 1$) and unknown cause ($n = 2$). Death ensued in 6.6% ($n = 21$) of the sample. A detailed list of demographics is found in Table 1.

BK viremia of ≥ 3 -log copies/mL was detected in 63 (19.7%) recipients. Of these, 47 (14.7%) were subsequently diagnosed with PP at a median time of 25 wk from initial screening. A renal biopsy was performed in 34 of these recipients and 18 (5.6% of the original sample) were confirmed to have DP. Two patients with DP progressed to graft failure and 4 developed AR within 90 d after reduction of immunosuppression.

The majority of the 319 patients included in the study (85.3%) never developed PyVAN. Time to first BK viremia was 190 d in patients with PyVAN and 235 d in those without. Graft loss occurred in 8.5% of patients with PyVAN vs. 4.8% of those without. Graft survival for 1-year, 3-year and 5-years were 99%, 95% and 92% respectively. A Kaplan-Meier curve of graft survival over time for recipients with and without PP (Figure 1) showed that survival was not significantly different between groups (logrank $P = 0.93$).

In a univariate analysis of recipients diagnosed with PP ($n = 47$) compared to recipients without PyVAN ($n = 272$), black race, DDKT and AR were significantly associated with PyVAN ($P < 0.10$). In a subsequent multivariate analysis, only DDKT (OR = 2.24; 95%CI

Table 1 Demographics and outcomes *n* (%)

Variable	All sample (<i>n</i> = 319)	PyVAN negative (<i>n</i> = 272)	PyVAN positive (<i>n</i> = 47)
Age (mean, yr)	53	51	53.1
Male	210 (65.8)	177 (65.1)	33 (70.2)
Black	86 (27.0)	67 (24.6)	19 (40.4)
Diabetes mellitus	86 (27.0)	71 (26.1)	15 (32.0)
CMV D+/R-	58 (18.2)	49 (18.0)	9 (19.1)
DDKT	174 (54.5)	140 (51.5)	34 (72.3)
Induction immunosuppression			
Thymoglobulin	118 (37.0)	97 (35.7)	21 (44.7)
Basiliximab	143 (44.8)	124 (45.6)	19 (40.4)
Daclizumab	56 (17.6)	50 (18.4)	6 (12.8)
Delayed graft function	58 (18.2)	47 (17.3)	11 (23.4)
Acute rejection	59 (18.5)	44 (16.2)	15 (32.0)
Graft loss	17 (5.3)	13 (4.8)	4 (8.5)
Death	21 (6.6)	15 (5.5)	6 (12.8)

DDKT: Deceased-donor kidney transplantation; PyVAN: Polyoma-virus associated nephropathy.

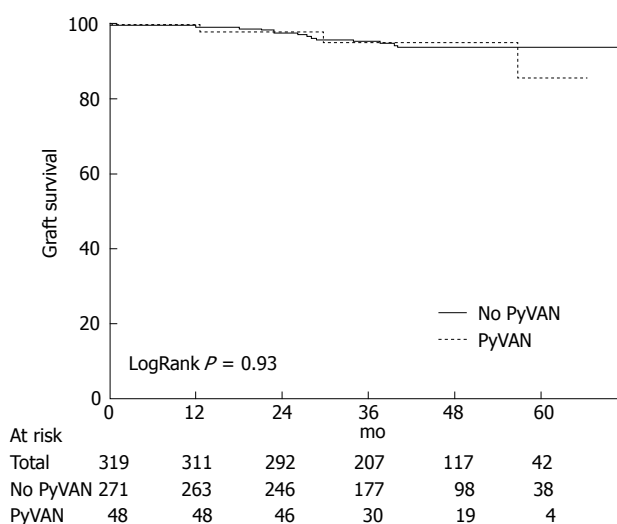


Figure 1 Kaplan-Meier Survival curve showing graft survival over time for recipients with and without presumptive polyoma-virus associated nephropathy. PyVAN: Polyoma-virus associated nephropathy.

= 1.1-4.54) and AR (OR = 2.42; 95%CI = 1.19-4.29) were significantly associated with PyVAN ($P < 0.05$). In this model, PyVAN was not associated with delayed graft function, graft loss or increased mortality. A full description covariates included in the fit-model is found in Table 2.

While the majority of patients with high-level viremia were found to have an initial BKVL above 4 log copies/mL, an initial BK viral load between 3 and 4-log copies/mL was reported in 27 transplant recipients, all of whom underwent reduction of immunosuppression, without administration of adjunctive anti-viral therapy. Of these, 16 (59%) never developed PyVAN while 11 (41%) developed PyVAN within a range of 11-39 wk. Among the 11 recipients with PyVAN, 4 were proven by renal biopsy and 7 were presumptive. Two of 27 recipients developed AR and none developed graft loss.

Since the BK PCR assay changed midway through the study, we compared the incidence of PyVAN when using the NIH assay (January 2009 to December 2010)

to the incidence when using the UW assay (January 2011 to December 2012). In a univariate chi-square analysis of all recipients with first BK viremia, 17/33 (52%) had PyVAN before the assay change versus 30/59 (51%) after the change ($P = 0.95$).

In addition, we reviewed BKVL data of patients with PP to evaluate for adherence or deviation from the set protocol for post-transplant viral load screening. Among 47 patients with PP, 16 patients underwent screening beyond the recommended interval during the study period and were found to have high-level viremia on belated screening. For 3 patients, screening was done within 10 d of recommended time point. A summary of patients in whom protocol deviation occurred is found in Table 3.

DISCUSSION

Though established guidelines recommend a reduction of immunosuppression at a sustained BK viremia of ≥ 4 -log copies/mL, studies vary significantly with regards to the implemented threshold. Cutoffs of any viremia^[16,17], of ≥ 3 -log copies/mL^[18] and of ≥ 4 -log copies/mL^[19] have been used with varying rates of PyVAN, graft loss and acute rejection. The incidence of PP in this study, using a lower threshold (≥ 3 -log copies/mL) of BK viremia for reduction of immunosuppression, was consistent with previously reported rates. In contrast to several investigations conducted in the last decade, which reported rates of graft loss of 15%-60% within 5 years of transplant, our incidence of graft loss, was 5.3%^[5,20-23]. The incidence of PyVAN-associated graft loss in this study (0.6%) was commensurate with more recently published data from 2009-2013, in which BK associated graft loss ranged from 0%-0.85%^[1,19,24-26]. Early reduction of immunosuppression in the setting of BK viremia, though potentially associated with decreased rates of graft loss due to BK nephropathy, carries the potential for increased rates of acute rejection. However, in this study, the incidence of acute rejection (18.5%) was also in keeping with previously reported rates^[19,25], suggesting that early reduction of

Table 2 Predictors of polyoma-virus associated nephropathy

Predictor	Univariate analysis			Multivariate analysis		
	PyVAN negative (<i>n</i> = 272)	PyVAN positive (<i>n</i> = 47)	<i>P</i> value	OR	CI	<i>P</i> value
Age (mean, yr)	51	53.1	0.343			
Male	177	33	0.493			
Black race	67	19	0.024 ^a	1.68	0.86-3.31	0.13
Diabetes mellitus	71	15	0.407			
CMV D+/R-	49	9	0.839			
DDKT	140	34	0.008 ^a	2.24	1.1-4.54	0.03 ^a
Thymoglobulin	97	21	0.237			
Basiliximab	124	19	0.511			
Daclizumab	50	6	0.412			
Delayed graft function	47	11	0.315			
Acute rejection	44	15	0.010 ^a	2.42	1.19-4.29	0.02 ^a
Graft loss	13	4				
Death	16	6	0.112			

^a*P* < 0.05. DDKT: Deceased-donor kidney transplantation; PyVAN: Polyoma-virus associated nephropathy.**Table 3 Protocol deviation among patients with presumptive polyoma-virus associated nephropathy¹**

Patient	Time point of protocol deviation post-transplant	Target days between serial screening	Actual days between serial screening	BKVL change (copies/mL)
1	Month 1 to month 3	60 d	100 d	ND to 1065190
2	Month 1 to month 3	60 d	138 d	ND to 17478
3	Month 9 to month 12	90 d	214 d	< 1000 to 1076120
4	Month 6 to month 9	90 d	393 d	< 1000 to 1269650
5	Month 6 to month 9	90 d	113 d	ND to 57982
6	Month 1 to month 3	60 d	134 d	ND to 392527
7	Month 3 to month 6	90 d	133 d	ND to 627218
8	Month 3 to month 6	90 d	108 d	ND to 82354
9	DOT to month 1	30 d	121 d	157939 at month 1
10	Month 3 to month 6	90 d	137 d	ND to 74389
11	Month 1 to month 3	60 d	179 d	ND to 28592
12	Month 1 to month 3	60 d	94 d	ND to 39000
13	DOT to month 1	30 d	58 d	17558 at month 1

¹Three patients with < 10 d of deviation from protocol were not included. ND: Not detectable.

immunosuppression may not necessarily increase the risk of acute rejection.

In the past decade, there has been a steady trend towards decreased rates of graft loss. This is thought to be the result of improved diagnostic tools including immunostaining and PCR, which better differentiate virus-induced nephropathy from acute rejection, as well as targeted interventions to promptly identify BK viremia and reduce immunosuppression earlier^[27]. A multitude of factors including the potency of induction and maintenance immunosuppressive regimens, demographic differences such as in age and race, frequency of BK viral load monitoring and use of adjunctive anti-virals may account for observed differences. The heterogeneity of these studies is further compounded by variation in the sensitivity, lower limit of detection of the BK virus PCR assay and most importantly a lack of equivalence of quantitation between different assays. Complicating matters is the presence of multiple viral subtypes, some of which (serotypes 3 and 4) are particularly prone to under-quantitation. In this study, we found no statistical difference in the number of patients with any viremia

when sequentially comparing two different molecular assays but results from laboratories using different assays have been shown to vary significantly, even when performed on the same sample^[15]. Since specific BK VL cutoffs are used to trigger interventions, assay variability is a critical issue and may indeed explain the variability in thresholds used across different transplant centers. A BK PCR standard that can be applied across laboratories is paramount in implementing a uniform BK viremia threshold for reduction of immunosuppression. In 2015, the World Health Organization (WHO) took steps to establish an international standard for BKV DNA nucleic acid amplification technique-based assays, using purified virions from BKV infected cell cultures^[28]. This standard, however, has not yet been widely adopted and additional *in-vitro* verification data and *in-vivo* clinical data are needed to ascertain its performance characteristics. Until then, performing serial testing on individual patients using the same assay within the same laboratory, eschewing over-interpretation of small viral load changes as biologically important and establishing center-specific viral load cutoffs to guide clinical decision making in local

patient populations will facilitate the interpretation of current BK viral load testing.

Certainly, adequate implementation of screening protocols is another critical factor in optimizing preventative strategies. In our study, a substantial number of patients with presumptive PyVAN did not adhere to the scheduled BKVL screening time-points. Strict adherence to screening protocol is likely to reduce the incidence of PyVAN by identifying viremia earlier and allowing for early interventions.

Instituting an early reduction of immunosuppression at ≥ 3 -log copies/mL, in the absence of adjunctive antivirals, was effective at preventing PyVAN in our center and may be associated with a lower incidence of graft-loss without an increased rate of acute rejection compared to published data. However, efforts to implement the WHO BK standard will be key in establishing a universal preventive strategy for PyVAN that is both highly effective and widely applicable.

COMMENTS

Background

Polyoma virus associated nephropathy (PyVAN) caused by BK virus (BKV) is a major complication occurring in 1%-10% of renal transplant recipients that is directly associated with graft loss and indirectly associated with graft rejection.

Research frontiers

Guidelines currently recommend prospective screening for BKV reactivation post-transplantation, with reduction of immunosuppression at > 4 -log copies/mL of BK virus. Additional research is needed to determine the best screening strategy.

Innovations and breakthroughs

The present study describes results of early reduction of immunosuppression (at ≥ 3 -log copies/mL) in the absence of antivirals. This strategy effective at preventing PyVAN and was associated with a lower incidence of graft-loss without a reciprocal increase in the incidence of acute rejection.

Applications

Early reduction of immunosuppression should be considered as a strategy for prospective screening for BKV reactivation post-transplantation.

Terminology

PyVAN is a disease of the kidney that results from reactivation of BK virus in the setting of immune suppression, leading to cytopathic effect on renal tubular cells and secondary inflammation.

Peer-review

The information provided by the authors adds to the existing knowledge on the subject and will prove useful to the transplant community.

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