Management of Kaposi sarcoma after solid organ transplantation: A European retrospective study

Julie Delyon, MD, PhD,[a] Clementine Rabate, MD,[b] Sylvie Euvrard, MD,[c] Catherine A. Harwood, MD, PhD,[d] Charlotte Proby, FRCP,[e] A. Tülin Güleç, MD,[f] Deniz Seçkin, MD,[f] Veronique Del Marmol, MD, PhD,[g] Jan Nico Bouwes-Bavinck, MD, PhD,[h] Carla Ferrándiz-Pulido, MD, PhD,[i] Maria Andrea Ocampo, MD,[c] Stephane Barete, MD, PhD,[j] Christophe Legendre, MD, PhD,[b] Camille Francès, MD, PhD,[k] Raphael Porcher, MD, PhD,[l] and Celeste Lebbe, MD, PhD,[a] the Skin Care in Organ Transplant Patients Europe (SCOP*E*) group

Paris and Lyon, France; London and Dundee, United Kingdom; Ankara, Turkey; Brussels, Belgium; Leiden, The Netherlands; and Barcelona, Spain

Background: Systemic therapeutic management of post-transplant Kaposi sarcoma (KS) is mainly based on 3 axes: reduction of immunosuppression, conversion to mammalian target of rapamycin (mTOR) inhibitors, chemotherapy, or a combination of these.

Objective: To obtain an overview of clinical strategies about the current treatment of KS.

Methods: We conducted a multicenter retrospective cohort study including 145 solid organ transplant recipients diagnosed with KS between 1985 and 2011 to collect data regarding first-line treatment and response at 6 months.

Results: Overall, 95%, 28%, and 16% of patients had reduction of immunosuppression, conversion to mTOR inhibitor, and chemotherapy, respectively. Patients treated with chemotherapy or mTOR inhibitor conversion were more likely to have visceral KS. At 6 months, 83% of patients had response, including 40% complete responses.

Limitations: The retrospective design of the study.

Conclusion: Currently available therapeutic options seem to be effective to control KS in most patients. Tapering down the immunosuppressive regimen remains the cornerstone of KS management. (J Am Acad Dermatol 2019;81:448-55.)

From the Department of Dermatology, Assistance Publique-Hôpitaux de Paris (AP-HP) Hôpital Saint Louis, Institut National de la Santé et de la Recherche Médicale U976, Université Paris Diderot, Sorbonne Paris Cité, Paris[a]; Service de Néphrologie-Transplantation Adultes, Hôpital Necker, AP-HP, and Université Paris Descartes, Paris[b]; Department of Dermatology, Edouard Herriot Hospital, Hospices Civils de Lyon[c]; Centre for Cell Biology and Cutaneous Research, Blizard Institute, Barts, and the London School of Medicine and Dentistry, Queen Mary University of London[d]; Dermatology, School of Medicine, University of Dundee[e]; Department of Dermatology, Başkent University Faculty of Medicine, Ankara[f]; Dermatology, Erasme Hospital, Université Libre de Bruxelles, Brussels[g]; Department of Dermatology, Leiden University Medical Center[h]; Department of Dermatology, Hospital Universitari Vall d'Hebron, Barcelona[i]; Sorbonne Université, Unit of Dermatology, AP-HP Pitié-Salpêtrière Hospital, Paris[j]; Sorbonne Université, Service de Dermatologie et Allergologie, AP-HP Hôpital Tenon, Paris[k]; and AP-HP, Centre d'Épidémiologie Clinique, Hôpital Hôtel-Dieu, and Centre of Research in Epidemiology and StatisticS (CRESS) Institut National de la Santé et de la Recherche Médicale U1153; Université Paris Descartes, Sorbonne Paris Cité.[l]

Dr Ocampo is currently affiliated with Dermatology Department, Sanitas Foundation, Colsanitas Clinic, Bogotá, Colombia.

Drs Delyon and Rabate are co-first authors, and Drs Francès, Porcher, and Lebbe are co-last authors.

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Correspondence to: Julie Delyon, MD, PhD, Dermatology Department, AP-HP Hôpital Saint Louis, 1 avenue Claude Vellefaux, 75475 Paris Cedex 10, France. E-mail: julie.delyon@aphp.fr.

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CAPSULE SUMMARY

- The therapeutic armamentarium against post-transplant Kaposi sarcoma is based on 3 axes: reduction of immunosuppression, conversion to mammalian target of rapamycin inhibitors, and use of chemotherapy.
- Therapeutic management of post-transplant Kaposi sarcoma is mostly based on reduction of immunosuppression and conversion to mammalian target of rapamycin inhibitor, inducing response in more than 80% of patients.

Because graft maintenance requires continuous immunosuppressive therapy, the risk of developing various types of cancer, particularly those associated with viral infections, is high in solid organ transplant recipients (OTRs).[1] Kaposi sarcoma (KS) is a lymphatic endothelium-derived tumor associated with human herpes virus type 8 (HHV-8) promoted by immunosuppression. Most cases of post-transplant KS arise as a result of HHV-8 reactivation triggered by drug-induced immunosuppression,[2,3] resulting in a 200-fold higher risk in OTRs than in the general population.[4] In the 1990s, mortality of KS was high, estimated to be 57% in patients with visceral extension of the disease.[5,6] Since then, post-transplant KS management has largely changed, with greater emphasis on minimization of immunosuppression rather than use of chemotherapy, but current mortality rates from post-transplant KS are unknown. Therapeutic management is still a challenge, because it requires controlling the disease while maintaining graft function.

Reduction of immunosuppression is an effective therapeutic option to reduce occurrence of malignancies in OTRs[7] but is limited by the risk of graft rejection. In KS, remission after decrease of immunosuppression alone was 30% to 50% in retrospective series.[6,8] Moreover, all immunosuppressive drugs do not carry the same risk of malignancies; particularly, mammalian target of rapamycin inhibitors (mTORis) have both immunosuppressive effects and direct antineoplastic effects.[9] Sirolimus has been associated with reduced occurrence of skin cancers, including KS, and nonskin malignancies to a lesser extent.[10-12]

Therapy for post-transplant KS has changed over the past 2 decades. In 2005, conversion to mTORis was shown to have a therapeutic effect: conversion from calcineurin inhibitors (CNIs) or purine antagonists to sirolimus induced responses in 72% to 100% of patients.[13,14] However, relapse and the apparent absence of remission in patients with visceral KS were reported in a significant proportion of patients treated with sirolimus.[14,15] Chemotherapy is usually required in patients with visceral involvement or rapidly evolving KS, and the use of chemotherapy has been best evaluated in AIDS-related KS.[16,17] The therapeutic armamentarium against post-transplant KS is now based on 3 axes: reduction of immunosuppression, conversion to mTORis, and use of chemotherapy. However, to our knowledge, neither comparative prospective trials nor retrospective studies have been conducted in post-transplant KS, and no consensus guidelines are available.

We conducted a retrospective study among expert European centers belonging to the Skin Care in Organ Transplant Patients, Europe (SCOP*E*) network to obtain an overview of the efficacy of treatment and prognosis in post-transplant KS.

MATERIALS AND METHODS

This multicenter retrospective study was conducted in 15 transplant centers in 6 countries (France, United Kingdom, Turkey, Belgium, Netherlands, and Spain). Ethics Committees in each country approved the study.

Patients

Solid OTRs with a pathologically confirmed diagnosis of post-transplant KS diagnosed between 1985 and 2011 were included. Patients with HIV were not included.

Clinical data were collected through a questionnaire completed from medical records, which included demographic data, transplantation data, characteristics of KS, KS therapeutic management, and response to treatment. KS extension was defined as visceral (at least 1 site among lymph node, pulmonary, or other visceral organ involvement) or not (for patients with cutaneous or mucosal only).

First-line therapeutic management was defined as systemic care given in the first 2 months after the KS diagnosis. Therapeutic options were reduction of immunosuppression, conversion to mTORis, chemotherapy, or a combination of these. Reduction

Abbreviations used:

CI:	confidence interval
CNI:	calcineurin inhibitor
CR:	complete response
HHV-8:	human herpes virus type 8
HR:	hazard ratio
IPTW:	inverse probability of treatment weighting
KS:	Kaposi sarcoma
mTORi:	mammalian target of rapamycin inhibitor
OS:	overall survival
OTR:	organ transplant recipient
PFS:	progression-free survival
PR:	partial response
SCOP*E*:	Skin Care in Organ Transplant Patients, Europe

of immunosuppression included dose reduction or drug withdrawal for corticosteroids, mycophenolate mofetil, azathioprine, or CNIs (cyclosporine, tacrolimus).

Response to KS first-line management at 6 months was classified as complete response (CR), partial response (PR), stable disease, or progressive disease after the Physician Global Assessment.[18]

Statistical analyses

Characteristics of treatment groups were compared using Fisher exact tests, Wilcoxon rank sum tests, or Kruskal-Wallis tests. Progression-free survival (PFS) was defined as the time delay between the first therapeutic decision to the first evidence of disease progression or death, whichever occurred first. Patients were otherwise censored at their last follow-up date. Overall survival (OS) was defined as the time between KS diagnosis and death. PFS and OS were assessed using Kaplan-Meier estimation. Graft loss was defined as the occurrence of a second organ transplantation or hemodialysis. The cumulative incidence of graft loss was analyzed in a competing-risks framework, with death as the competing event.

Two approaches were used to account for confounding resulting from baseline imbalance in prognostic factors in the comparison of PFS between patients who did and did not receive mTORis. First, inverse probability of treatment weighting (IPTW) was used to reconstruct pseudopopulations with similar baseline characteristics. Adjusted Kaplan-Meier curves were then estimated,[19] and a Cox model with robust variance estimator was used for comparison. Second, Cox models were used for regression adjustment. Variables used were the predefined potential prognostic variables of mucosal KS, lymph node involvement, symptomatic visceral KS, cytomegalovirus infection, cytomegalovirus prophylaxis, and herpes simplex virus prophylaxis. HHV-8 viral load was not used owing to too many missing data. Missing covariates were handled through multiple imputation by chained equations.[20,21] Fifty imputed data sets were created and analyzed separately. Results were then pooled over the imputations according to the Rubin rule. Statistical analyses were performed using R 3.2 software (The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patient characteristics

The study enrolled 145 patients with post-transplant KS diagnosed between February 1985 and April 2011 from France (n = 109), United Kingdom (n = 14), Turkey (n = 9), Belgium (n = 7), Netherlands (n = 4), and Spain (n = 2). There were 91 patients diagnosed with KS after 2005, when the first study highlighting the benefits of mTORis in post-transplant KS was reported.[13] Baseline characteristics are summarized in Table I. Patients were a median age of 53 years, 76% were men, and 89% were kidney transplant recipients.

KS developed within a median time of 17 months after transplantation (interquartile range, 9-38 months). Prior primary HHV-8 infection was reported in 2 patients only. All patients were receiving immunosuppressive therapies, including a CNI for 92%. Four patients had already been receiving mTORi therapy before the KS diagnosis.

Visceral KS was present in 51% of patients, which was symptomatic for 20 patients (14%). Pulmonary KS was reported in 20% of patients.

First-line therapeutic management

First-line therapeutic management was highly variable between patients (Fig 1). Nevertheless, 95% of patients shared the common feature of having reduction of immunosuppression, which included dose reduction or drug withdrawal for CNI, mycophenolate mofetil, azathioprine, or corticosteroids. Conversion to mTORi was performed in 28% of patients, mostly in association with a reduction of other drugs. Among the 91 patients whose KS was diagnosed after 2005, 67% had conversion to mTORi versus 3% among patients before 2005.

Chemotherapy, usually required for severe KS,[22,23] was used as first-line therapy for 23 patients (16%), in addition to reduction of immunosuppression in 12 (8%) or conversion to mTORi in 10 (7%). Cytotoxic agents included liposomal doxorubicin (n = 9), bleomycin monotherapy (n = 4), doxorubicin, bleomycin, and vinblastine (n = 5), vinblastine

Table I. Characteristics of patients and Kaposi sarcoma

Characteristics*	Overall population (N = 145)
Patient characteristics	
Age, y	53 (44-62)
Male sex	110 (76)
Region of birth	
Sub-Saharan Africa/Caribbean	76 (56)
Mediterranean	47 (35)
Northern Europe	13 (9)
Not available	9
Transplanted organ	
Kidney	127 (89)
Heart	3 (2)
Liver	5 (3)
Lung	3 (2)
Other	5 (4)
Not available	2
Induction therapy	
Yes	102 (81)
No	24 (19)
Not available	19
Treatment of induction	
Steroids	76 (60)
Antithymocyte globulin	51 (40)
Anti—interleukin-2 receptor	33 (26)
OKT3	8 (6)
Rejection episodes	
No	79 (59)
Yes	56 (41)
Not available	10
Treatment of rejection	
Steroids	47 (70)
Antithymocyte globulin	10 (15)
OKT3	3 (5)
Rituximab	1 (2)
Intravenous immunoglobulin	3 (11)
KS characteristics	
Immunosuppressive drugs at KS diagnosis	
CS + CNI + PI	109 (76)
CS + CNI	20 (14)
CS + PI	8 (6)
CS + mTORi + CNI or PI	4 (3)
Other†	4 (3)
KS extension	
Cutaneous only	60 (42)
Mucosal (+/− cutaneous, w/o visceral)	11 (8)
Visceral (+/− cutaneous/mucosal)	73 (50)
Not available	1
Lymph node involvement	39 (33)
Gastrointestinal involvement	47 (36)
Pulmonary KS	29 (20)
HHV-8 detection	
Positive HHV-8 viral load	29 (54)
Positive LANA IHC	88 (98)
Positive latent IF serology	74 (91)

CNI, Calcineurin inhibitor; *CS*, corticosteroids; *HHV-8*, human herpes virus type 8; *IF*, immunofluorescence; *IHC*, immunohistochemistry; *KS*, Kaposi sarcoma; *LANA*, latency-associated nuclear antigen; *mTORi*, mammalian target of rapamycin inhibitor; *OKT3*, anti-cluster of differentiation 3 antibody; *PI*, purine inhibitor; *w/o*, without; *+/−*, with or without.
*Continuous data are reported as median (interquartile range) and categorical data as number (%).
†Other immunosuppressive drugs at KS diagnosis: no treatment (n = 1), CNI alone (n = 1), CNI + PI (n = 1), unknown treatment (n = 1).

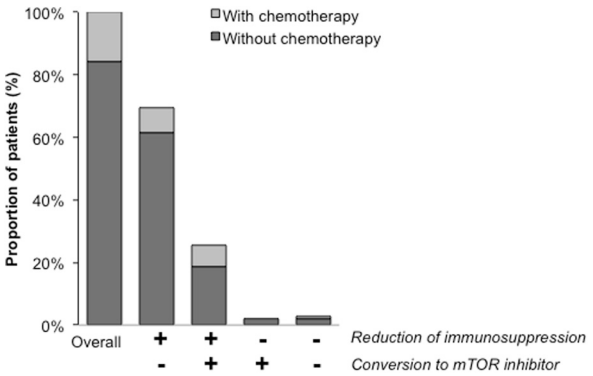

Fig 1. First-line treatment combination for post-transplant Kaposi sarcoma. Strategies included the combination of reduction of immunosuppression, conversion mammalian target of rapamycin (*mTOR*) inhibitors, and chemotherapy.

(n = 2), paclitaxel (n = 1), bleomycin and vinblastine (n = 1), and vindesine (n = 1).

In addition, local treatments were reported in 15 patients, comprising surgery in 8, radiotherapy in 5, and imiquimod in 2.

Characteristics associated with first-line therapeutic management of KS

Given that 95% of patients had reduction of immunosuppression, we defined 4 groups of patients among the therapeutic options of conversion to mTORi and chemotherapy use. Specifically, group 1 (n = 92), no mTORi conversion and no chemotherapy; group 2 (n = 13), no mTORi conversion with chemotherapy; group 3 (n = 30), mTORi conversion and no chemotherapy; group 4 (n = 10), mTORi

Table II. Characteristics of patients in the 4 first-line treatment groups

Variable*	First-line treatment of KS				
	No conversion to mTOR inhibitor		Conversion to mTOR inhibitor		
	Group 1: No chemotherapy	Group 2: With chemotherapy	Group 3: No chemotherapy	Group 4: With chemotherapy	*P*
Age, mean (SD), y	52.8 (13.3)	42.2 (17.7)	55.9 (13.7)	47.5 (10.4)	.010
Male sex	70 (76)	12 (92)	22 (73)	6 (60)	.34
Sub-Saharan/Caribbean origin	43 (49)	4 (31)	15 (58)	9 (90)	.030
Time to KS diagnosis, median (IQR), mo	19 (10-40)	14 (8-39)	15 (8-35)	16 (10-24)	.76
Mucosal KS	14 (15)	2 (15)	6 (20)	2 (20)	.87
Lymph node involvement	18 (20)	5 (38)	7 (23)	9 (90)	<.0001
Symptomatic visceral KS	5 (6)	5 (38)	4 (14)	6 (67)	<.0001
Herpes simplex virus prophylaxis	23 (33)	5 (56)	17 (61)	7 (70)	.021
Overall	92 (63)	13 (9)	30 (21)	10 (7)	—

IQR, Interquartile range; *KS*, Kaposi sarcoma; *mTOR*, mammalian target of rapamycin.
*Continuous variables are presented as shown and categorical variables as number (%).

conversion with chemotherapy. Group 1 included almost exclusively patients with reduction of immunosuppression (97%), which included dose reduction or withdrawal for CNI (n = 54), azathioprine (n = 39), mycophenolate mofetil (n = 11), and corticosteroids (n = 16). Characteristics of patients in these 4 subgroups are summarized in Table II.

Some characteristics related to KS extent were significantly different between groups. The proportion of patients with symptomatic visceral KS or lymph node involvement was significantly higher in group 4 than in groups 1, 2, and 3 ($P < .0001$). Chemotherapy was the first-line treatment in 55% of patients with symptomatic visceral KS versus 10% of patients without symptomatic visceral KS. Thus, group 4 was mostly composed of patients with visceral KS: 67% and 90% of patients had symptomatic visceral KS and lymph node involvement, respectively, compared with 6% and 20% of patients in group 1. Irrespective of chemotherapy use, patients who received mTORis also had more advanced disease, with a higher proportion of symptomatic visceral lesions ($P = .027$), more lymph node involvement ($P = .051$), and more visceral lesions ($P = .035$).

KS response to first-line therapeutic management

Among 137 evaluable patients, 83% had response to the treatment at 6 months, including 40% with CR and 43% with PR (Fig 2). CR occurred more frequently in patients without visceral involvement (47%) than in patients with visceral disease (30%), whereas PR was more frequent in patients with visceral involvement (51% vs 31%). At 6 months, 11% of patients experienced progressive disease. For the 75 patients who had visceral disease, 55 were treated with only reduced immunosuppression or

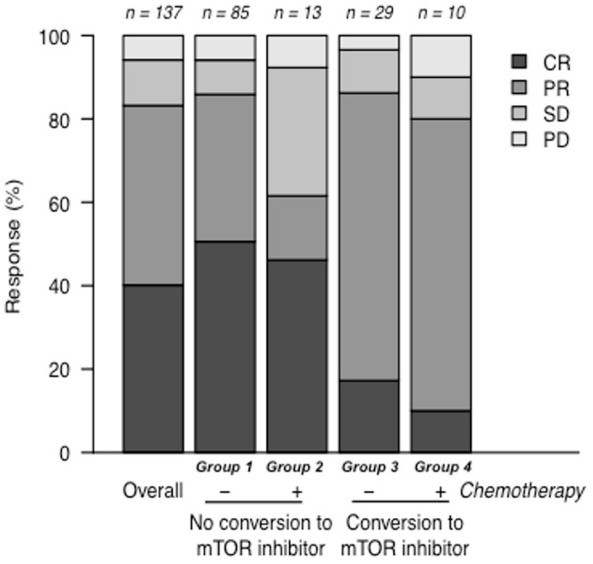

Fig 2. Responses at 6 months to first-line treatment, classified as complete response (*CR*), partial response (*PR*), stable disease (*SD*), and progressive disease (*PD*) in the response-evaluable population (n = 137), are plotted for each treatment group. *mTOR*, mammalian target of rapamycin.

mTORi, and 18 received chemotherapy; of these, 71 patients were evaluable for response. Of the 18 patients treated with chemotherapy, 5 (28%) had a complete response and 8 (44%) had a partial response. Among the 53 evaluable patients with visceral disease not treated with chemotherapy, 17 (32%) had PR and 29 (55%) had CR.

The 2 most used therapeutic options, which were reduction of immunosuppression (97% of patients in group 1), and reduction of immunosuppression associated with conversion to mTORi (90% of patients in group 3), had a similar response rate of 86%. Conversion to mTORi induced 17% CR and 69%

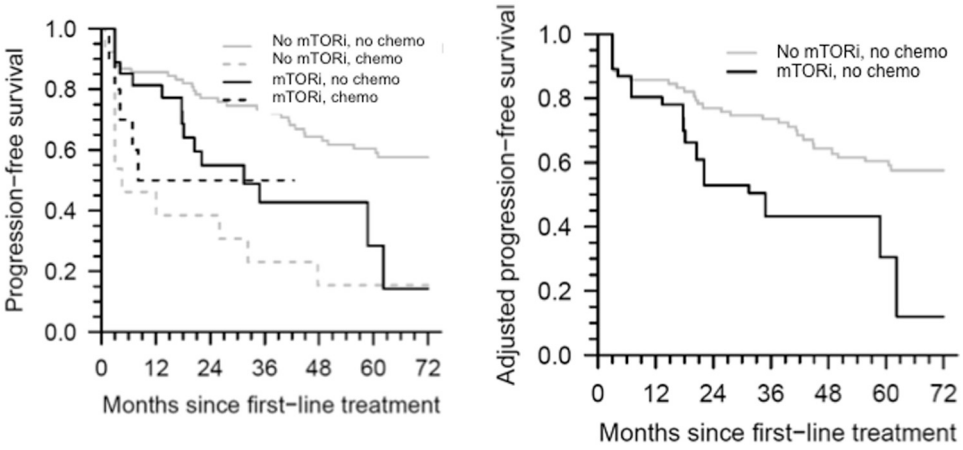

Fig 3. Survival analyses for patients with post-transplant Kaposi sarcoma. **Left**, Unadjusted Kaplan-Meier curves for progression-free survival according to first-line treatment. **Right**, Adjusted Kaplan-Meier curves for progression-free survival between patients receiving mammalian target of rapamycin inhibitors (*mTORis*) or not. The group of patients receiving chemotherapy was too small to be included in the adjusted analyses.

PR. However, patients who did not receive mTORi achieved more CR (P = .0002) but not more overall responses (CR + PR) (Fig 2).

Bearing in mind that patients' characteristics were different between treatment groups (Table II), response rates were similar with chemotherapy. In patients treated with conversion to mTORi, 17% had CR and 69% had PR, whereas in those who had additional chemotherapy, 10% had CR and 70% had PR. Among patients without conversion to mTORi, response rates were lower for those treated with chemotherapy (62% vs 86%).

Patients with KS relapse or who progressed on first-line treatment (n = 52) were treated with chemotherapy (25 [52%]), additional reduction of immunosuppression (24 [46%], or switch to mTORi (15%), or a combination of these.

Survival

The median follow-up time from the KS diagnosis was 91 months (7.6 years; range, 1-276 months). During follow-up, 37 patients died, including 4 deaths of KS (3%) and 3 of unknown causes. OS was 82% (95% confidence interval [CI], 75%-89%) at 5 years and 64% (95% CI, 54%-75%) at 10 years. OS was not related to KS extent at diagnosis.

Differences in PFS were found between the 4 groups (P = .0008) (Fig 3, *B*), with better PFS in group 1 patients. However, treatment groups differed according to patient baseline characteristics, specifically the extent of disease (Table II). To account for this confounding resulting from baseline imbalance in potential prognostic factors, IPTW estimators and regression adjustment were used to compare PFS between patients who did and did not receive mTORi (but not chemotherapy, because this group was too small sample size). Results were similar for unadjusted, IPTW and adjusted analyses, with hazard ratios (HRs) for mTORi versus no mTORi of 2.18 (95% CI, 1.18-4.05), 2.22 (95% CI, 1.23-4.03), and 2.45 (95% CI, 1.29-4.645), respectively (Fig 3).

Graft survival

Similar analyses were performed to study the risk of graft failure related to KS management. Graft loss occurred in 34 patients. Across the 4 groups, the cumulative incidence of graft loss was not different (Gray test P = .99). IPTW analysis showed the HR of graft rejection for mTORi versus no mTORi was not significantly increased or decreased (HR, 0.69; 95% CI, 0.20-2.34).

DISCUSSION

In this study, patient data from 15 centers across Europe were pooled to obtain an overview of post-transplant KS management and responses to treatment. Treatment was mostly based on immunosuppression reduction and conversion to mTORi, inducing response in more than 80% of patients. KS-related deaths rarely occurred, suggesting that KS can be effectively controlled.

mTORis have been included in the armamentarium of immunosuppressive drugs since 2000.[24] In 2005, Stallone et al[13] demonstrated that mTOR inhibitors induced CR in 100% of 15 patients with post-transplant KS. This effective strategy based on CNI withdrawal and switch to mTORi was confirmed in other studies,[14,25-27] although Lebbé et al[14]

reported a significant proportion of relapses (3 of 14 patients) and resistance in patients with visceral KS. Switch to mTORi became part of the standard management strategy of post-transplant KS.[22,23] In the present study, conversion to mTORi induced responses in more than 80% of patients. However, these patients—who certainly had more visceral KS—experienced fewer CRs than those who did not receive mTORis. Statistical maneuvers to adjust for important prognostic factors, such as disease extent, were undertaken. Despite this, the long-term risk of disease progression remained significantly higher in OTRs who received mTORis.

Reduction of immunosuppression is still the cornerstone of post-transplant KS management. Immunosuppression was minimized in almost all patients in this study, and 50% of CRs were achieved solely by a decrease of immunosuppression. Clinical benefits reported in mTORi conversion or chemotherapy groups might be partially attributable to the decrease of immunosuppression. Moreover, in contrast to prospective studies, reduction of immunosuppressive therapies is highly heterogeneous in retrospective studies. Beyond the level of immunosuppression, the type of regimen also contributes to the risk of post-transplant malignancies. CNIs were found to have direct oncogenic properties,[28-30] and CNI withdrawal was associated with risk reduction of post-transplant malignancies.[10] Conversely in KS, there is a growing amount of evidence suggesting that mTORis have direct antitumor cell effects that are independent of the immune system.[31,32] In contrast, everolimus was unsuccessfully tested in classic KS, suggesting that immunosuppressive effects of mTORi could override its antineoplastic properties in immunocompetent patients, whereas this appears not to be the case in patients who are immunocompromised.[33,34]

Chemotherapy is usually required in cases of extensive or symptomatic visceral KS.[22] In our cohort, chemotherapy was used for advanced KS (visceral involvement or rapid progression, or both) in less than 20% of patients. Response rates were increased in association with mTORi conversion, suggesting that the combination of mTORi and short-term chemotherapy could be an effective strategy in patients with visceral KS.

To our knowledge, this study represents the largest case series to focus on post-transplant KS and the first to report first-line practices. The retrospective design limits detailed comparison of data because we could not be rule out that the different outcomes in treatment groups were due to unmeasured confounding factors. Screening for KS extension at diagnosis was performed according to local practices and might be heterogeneous between centers.

Missing information, such as KS treatment received after the first 2 months, limited the quantity and quality of interpretable data. For instance, data regarding the optimal time to conversion to an mTORi after the KS diagnosis or the total amount of corticosteroids received after the KS diagnosis, which is associated with KS occurrence and outcome,[35] could not be studied in detail.

Finally, the study population was probably heterogeneous because of the extended inclusion period during which practices regarding immunosuppressive regimens and KS therapeutic strategy have evolved, particularly before and after 2005.[13]

CONCLUSION

This study provides insight into clinical practices in post-transplant KS management, which is based on reduction of immunosuppression in addition to conversion to mTORi, or chemotherapy, or a combination. The signal from our data that mTORi conversion may be associated with a higher risk of progression is complicated by multiple potential confounders, including KS extent, but is an indication that further prospective studies are now warranted to precisely assess the long-term benefits of conversion to mTORis in the management of post-transplant KS.

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