Managing immunosuppressive therapy in potentially cured post-kidney transplant cancer

On behalf of the ESOT Transplant Learning Journey 2020 working group[1] on post-transplant cancer

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Abbreviations

CNI, calcineurin inhibitors; mTORi, mTOR inhinitors; Tac, tacrolimus; CsA, cyclosporine A; SRL, sirolimus; EVL, everolimus; MMF/MPA mycophenolate mofetil/mycophenolate acid; AZA, azathioprine; SOT, solid organ transplant; KTRs, kidney transplant recipients; PTLD, post-transplant lymphoproliferative disease; RCT, randomized control trial; eGFR, estimated GFR (Glomerular filtration rate)

Introduction

Kidney transplant recipients (KTRs) have increased incidence of de novo cancers, which contributes to their excess mortality when compared to the general population. Cancers at highest risk are those that are virus-induced such as post-transplant lymphoproliferative disease (PTLD) and Kaposi Sarcoma, and those that are caused both by impaired immune surveillance and by direct DNA damage by anti-rejection drugs themselves, such as skin and lip cancers[1]. However, many other cancer types occur more frequently in transplant patients[2].

When an individual is faced with potentially curable cancer, treatment options often include surgery with or without concomitant or (neo-)adjuvant radiotherapy, chemotherapy, hormone therapy or immune checkpoint therapy. Online calculators for the general population are available which, by using patient and tumor characteristics, provide recurrence risk and survival probability that can guide oncological counseling and help deciding on the optimal treatment strategy. However, difficult it may be for anyone to be confronted with this ordeal; being a transplant recipient adds even more complexity and challenges. The immunosuppressive drugs needed to prevent transplant rejection increase the risk of cancer treatment complications such as impaired wound healing and infections. In addition, the impaired immune system may have a negative impact on cancer control and treatment response. Calculators based on the general population may therefore overestimate prognosis in transplant recipients. This is illustrated by the Transplant Cancer Match study, which linked national U.S. transplant and cancer registry data to examine the survival after cancer diagnosis among solid organ transplant (SOT) recipients[3]. The study showed that for most cancer types, transplant recipients have an elevated risk of dying from their cancer compared to non-transplant cancer patients, even after adjustment for cancer stage and treatment, suggesting that apparently curable cancers with seemingly good prognosis may be more susceptible to micro-metastases in immunosuppressed individuals. Furthermore, many of the cancer types with strongly increased cancer-specific mortality among solid organ transplant recipients are cancer types in which immune control is believed to be critical[4], thus supporting the hypothesis of immunosuppression-induced reduced effectiveness of immune surveillance. However, not every tumor is equally susceptible to immunosuppression. For instance, Yanick et al[5] examined in over 200000 patients from US, the incidence of different cancers during graft function (first and second transplant), and graft non-function (graft failure after first and second transplant, that is, when patients are off-immunosuppression): the incidence of kidney, and thyroid cancer was not higher during periods of immunosuppression compared to periods off-immunosuppression). Moreover, in the Australian-New Zealand study from Au et al[6] the Authors showed that KTR have an elevated relative risk of dying from several cancer types compared to the general population, with highest standardized mortality ratio's (SMR) for lymphoma, kidney cancer and melanoma (SMR being 10.7, 7.8 and 5.8, respectively), whereas mortality from prostate cancer is not increased.

After having undergone treatment for cancer with curative intent, the transplant recipient and transplant physician face the difficult decision on how to continue with the antirejection therapy. Although reducing the overall immunosuppressive load and/or switching to an alternative drug regimen may potentially be of great benefit to avoid cancer recurrence, this should be balanced against the risk of rejection and the risk of severe

adverse events. Unfortunately, little is known, on the optimal immunosuppressive strategy in organ transplant recipients after treatment for post-transplant cancer with curative intent. There are cases where cancer type and potential efficacy of the anti-cancer treatment are associated with a relatively low risk of cancer recurrence. That may happen in patients with stable graft function and young age, who may have a relatively large lifetime risk of graft rejection. Assessment of benefit and risks of immunosuppressive reduction or change to a difference maintenance anti-rejection treatment in this setting may be particularly challenging and should be based on a shared decision making. Shared decision making is a patient-centered discussion which concentrates on how alternative therapeutic options may impact the specific patient, and considers these impacts in light of the patient's particular considerations and specific risk factors[7]. The question on how to continue with the immunosuppressive therapy can be generalized to settings in which anti-rejection maintenance therapy had been reduced during the treatment for cancer and the transplant physician has to decide whether to resume standard therapy, to maintain a reduced immunosuppressive regimen, or to switch to a different anti-rejection regimen.

During the Transplant Learning Journey (TLJ) 2020, an initiative by the European Society of Organ Transplantation (ESOT), one of 6 working groups, including two nephrologists, one hematologist, and one methodologist discussed this topic at an online platform with a large multidisciplinary audience, and reviewed the available evidence. In this paper, we first present the results of a systematic literature search which tried to answer the following 2 questions: 1) Should we decrease the overall anti-rejection therapy in potentially cured post-kidney transplant cancer (excluding non-melanoma skin cancer)? 2) Should we switch to mammalian target of rapamycin inhibitors (mTORi) in potentially cured post-kidney transplant cancer (excluding non-melanoma skin cancer)? The literature search revealed that robust data to answer these questions are lacking, implying that evidence-based recommendations cannot be made. Despite the lack of solid evidence, practical advice for transplant professionals and their patients on the management of immunosuppressive therapy in potentially cured post-transplant cancer is considered to be of great clinical value. Therefore, we additionally provide an extensive overview of the indirect evidence on the possible benefit and risks of immunosuppressive medication alterations, and provide a summary that could be used for shared decision making.

Methods

The PICO model was used to formulate clinical questions. Separate bibliographic searches were developed for each of the clinical questions by experienced staff from the Centre for Evidence in Transplantation, University of Oxford. Systematic searches were conducted in the Transplant Library (www.transplantlibrary.com), Medline and Embase. Full details of the searches including search dates can be found in the Appendix. Searches consisted of a mixture of free text and controlled vocabulary terms. We included all solid organs, all study designs including systematic reviews, randomized controlled trials, registry analyses, observational studies and clinical practice guidelines, and both adult and paediatric populations. Studies were excluded if

cancer was a non-melanoma skin cancer. Search results were limited to the English language and studies published from the year 2000.

Results of the systematic literature search

Question 1: Should we decrease the overall anti-rejection therapy in potentially cured post-kidney transplant cancer (excluding non-melanoma skin cancer)?

The first step of the literature search focused on solid cancers. There are no systematic reviews or randomized controlled trials on this topic. Only two small (n=87 and n=110, respectively), retrospective cohort studies were identified[8,9] comparing outcomes in KTR with post-transplant cancer between those remaining on standard immunosuppression and those who underwent reduction of immunosuppression. However, no clear conclusions could be drawn from these studies because of the low number of patients, high heterogeneity of cancer types and cancer stages, varying immunosuppressive regimens and a high risk of indication bias, because the patients who were switched to a reduced immunosuppressive regimen are more likely to be those with an inferior prognosis (supplementary file). A second literature search, specifically on post-transplant lymphoproliferative disorder (PTLD) yielded no studies that matched the inclusion criteria of our search strategy; we found only small, retrospective studies with a large heterogeneity in terms of PTLD type and treatment as well as of immunosuppression reduction at the time of PTLD diagnosis, with no studies specifically examining outcomes according to the choice of immunosuppression áfter completing PTLD treatment.

Question 2: Should we switch to mammalian target of rapamycin inhibitors (mTORi) in potentially cured post-kidney transplant cancer (excluding non-melanoma skin cancer)?

There are no systematic reviews or RCTs on this topic. Only two small retrospective studies[10,11] were found which (partly) met the search criteria. Based on their retrospective nature, the low number of patients, the high heterogeneity in cancer types and stages, varying immunosuppressive regimen and risk of indication bias, no clear conclusions can be drawn from these studies. A second literature search, specifically on post-transplant lymphoproliferative disorder (PTLD) again yielded only very small retrospective case series which did not specifically described the outcomes of changing to mTORi versus maintaining on a regimen without mTORi áfter completing of PTLD therapy .

Discussion

Should we decrease the overall anti-rejection therapy in potentially cured post-kidney transplant cancer (excluding non-melanoma skin cancer)?

Reducing overall maintenance anti-rejection treatment, to an extent that depends upon cancer type, stage and other factors, has been the traditional approach used for transplant recipients with a history of non-skin cancer treated with a curative intent, although robust studies to evaluate the safety and efficacy of such strategies are lacking. When reducing the overall immunosuppressive load, it is not clear which agent should be preferentially reduced or stopped. Transplant recipients are generally treated with multidrug maintenance therapy, and some have additionally received antibody induction therapy or treatment for rejection. It is therefore extremely difficult to discern the impact of any individual immunosuppressive agent on cancer development and cancer control and to distinguish the effect of a particular drug from the effect of the overall immunosuppressive burden. The calcineurin-inhibitors (CNI) cyclosporine A (CsA) and tacrolimus (Tac) have been shown to upregulate transforming growth factor β1 (TGF- β1)[12] and vascular endothelial growth factor (VEGF)[13], both of which are known to contribute to cancer growth and angiogenesis[14]. They also suppress anti-oncogenic genes (p53 via NFAT-ATF3)[13,14]. CNIs inhibit the T-bet-dependent antitumor response of CD8+ T Cells[15] and are the strongest inhibitors of priming of CD4+ T cells. T cells are the main subset involved in immunosurveillance against tumors[16] as shown by the successful introduction in oncology of the checkpoint inhibitors namely, CTLA-4 inhibitors, which promote CD4+ T cells priming in lymph nodes, and of PD1/PD-L1 inhibitors which prevent CD8+ T cell exhaustion in peripheral tissue[16]. By blocking those two key mechanisms of T cell peripheral tolerance, immune checkpoint inhibitors act by unleashing cytotoxic T cell against cancer[16]. In fact, a randomized control trial (RCT) in KTR from the 90s[17] to standard (200 mg/mL) or reduced (100 ng/mL) blood trough level, showed that CsA had a dose-dependent effect on inducing skin and non-skin cancer. In contrast, 20-years follow-up post-hoc analysis of another RCT[18] showed no difference in skin and non-skin cancer between KTR maintained on CsA and those taking azathioprine (AZA) and steroids. However, AZA is one of the drugs which is most strongly associated with the incidence of skin cancer, with mechanisms that are independent on immunosuppression, as AZA sensitizes cells to UV-induced damage through the incorporation of a metabolite into DNA[19] and it also associated with an increased risk of other malignancies such as lymphoma and urinary tract cancers in non-transplanted patients[20]. It is unclear if the risk of developing cancer is different with CsA versus Tac. For example, a large international registry analysis showed a higher risk of post-transplant lymphoma with Tac than with CsA in KTR, although there was no difference in risk in the same study between Tac and CsA in liver transplant recipients, despite a higher number of cases in the liver transplants[21]. Reduction of trough blood levels of CNI below the traditional lower bounds may be most effective strategy to prevent cancer recurrence but also the least safe strategy with regard the risk of rejection. In fact, a RCT in which stable low-risk steroid-free KTRs between 4-12 month post-transplantation were

randomized to a Tac 50% reduction (target trough level >3 ng/mL) or no change dose (target trough levels 7-12 ng/mL), showed that Tac reduction is associated with a sharp increased risk of acute rejection at 1 year (11 vs 2%), and development of donor-specific antibodies (6 vs 0%)[22]. As for mycophenolate mofetil (MMF), recent large registry studies have not found differences in cancer incidence in regimens with or without MMF[23]. Likewise, the use of steroids is also not associated with increased cancer incidence[24].

PTLD. Several immunosuppressants have been described as inducing more PTLD than the others. In 25,000 renal transplant recipients, in association with an antimetabolite (AZA or MMF), Tac induced twice as many PTLDs as CyA[21]. In 115000 renal transplant recipients, the combination of an mTORi inhibitor with Tac caused 40% more PTLDs than MMF[25] and in general MMF appears to be less responsible for PTLD after renal transplant than AZA[26]. The current management of PTLDs is fairly codified and the results are remarkable, with a median overall survival greater than 6 years[27]. The standard of treatment includes induction with rituximab followed by either rituximab monotherapy in the event of complete remission, or a combination of the R-CHOP type, however, in rare cases, the decrease in immunosuppression alone results in complete remission[28]. In the latter case, it seems preferable to keep the immunosuppression as low as possible throughout the patient's follow-up. In the other cases, which are the most frequent, an additional reduction in immunosuppression after remission of PTLD is of no interest, the rate of relapse being limited[29]. Conversely, a re-increase or modification seems possible since some studies have shown very rare relapses after a new renal transplant[30,31]. However, currently, there is no recommendation on how to modify the immunosuppression and the time between the response of PTLD and this modification.

Should we switch from CNI to a mTORi-based CNI-free regimen?

The rationale for switching to a mTORi is based on several indirect arguments[32,33]. First, the mTOR pathway is involved in cellular growth and proliferation[32,34] and has a well-described role in carcinogenesis[32]. Based thereupon, mTORi are sometimes used for treating cancer: everolimus (EVL) is an FDA approved drug for treatment of certain breast cancers, certain neuroendocrine tumors and renal cell carcinoma. It should be noted that the EVL dose for cancer treatment namely 5mg or, most often 10 mg daily, often yields EVL blood trough levels of 10ng/mL or above[35,36]. The EVL anti-cancer effect is dose-dependent. A meta-analysis[36] has shown that that a two-fold increase in blood trough levels is linked to an increased reduction in tumor size and that EVL blood levels of ≥ 10 ng/mL could be used as a cut-off value for efficacy. Indeed, in cancer literature a therapeutic window of 10 to 26ng/mL has been proposed for EVL[35]. Such levels are higher than those that were targeted to prevent rejection after SOT in CNI-free regimens as in the Zeus RCT[37,38], and are generally poorly tolerated. In the Zeus RCT, blood trough levels, which were targeted to 8ng/mL (range: 6-10), were eventually kept on average at the lower bound of the intended range (6.6ng/mL), which was on average achieved with 3.4 mg/daily[37] . Of note, in association with CNI, EVL blood trough levels are kept even at lower levels (5.5ng/mL; range: 3-8 ng/mL)[39]. Such blood targets are commonly achieved with a dose of only 3.0 mg daily with Tac and 1.5mg daily with CsA due to drug-to-drug interaction between EVL and CsA. Second, there is

evidence from meta-analyses of RCTs[40,41] and large registry analyses[42], that SOT recipients on mTORi have a reduced risk of developing non-melanoma skin cancers. Based on these clinical findings, the question arises if mTORi could also decrease the risk of developing other post-transplant cancers. The only individual-level patient data meta-analysis of RCTs on CNI-free mTORi-based maintenance regimens published so far[40] showed that, on more than 5800 KTRs from 21 RCTs, regimens containing sirolimus (SRL) caused a 56% reduction in the rate of non-melanoma skin cancer (hazard ratio: 0.44; 95 percent confidence interval: 0.30 to 0.63). There was, however, no difference in risk of developing other cancers between patients on SRL versus controls in the overall study population, although the subgroup analysis on conversion RCTS from CsA to SRL (as opposed to RCTs with *de novo* SRL) did show a 48% reduction in the risk of other cancers (hazard ratio; 0.52; 95 percent confidence interval: 0.38 to 0.69)[40]. However, despite the possible reduction in the incidence of cancer in some settings, it should be noted that CNI-free mTORi-based regimens were associated with an increased risk of death of +20% after four year post-randomization, mainly due to infection and cardiovascular disease[40]. A meta-analysis in KTR showed that converting from a CNI to a CNI-free mTORi containing regimen (during the first year post-transplant) almost doubled the risk of rejection compared to continuing on CNIs (RR 1.86 (95% CI 1.44-2.40))[43]. Furthermore, 22 % discontinued mTORis because of adverse events[43]. The risk of graft loss might depend on the baseline level of renal function. In the CONVERT study[44], the largest RCT on conversion from CsA to SRL ever performed (830 patients randomized 2:1, 6 months to 10 years post-transplant, to switch from CsA to SRL with a blood target trough level of 8-20ng/mL) showed that the conversion was safest in patients with eGFR > 40 mL/min and urinary protein-to-creatinine ratio ≤0.11 gr/gr. The most recent study (ZEUS RCT) on the conversion from CsA to EVL (300 patients randomized at 4 months post-transplant on switching from CsA to EVL with target 6-10ng/mL, or continuing CsA) have not confirmed the increased risk of death, after a follow-up of five years[38]. For what regards the risk of rejection, some concern still remains, as in a study a study carried out on a subset of 127 German patients enrolled in the same RCT or in a similar RCT (CRAD001ADE13-trial) showed that, at 5 year post-transplantation, the risk of developing donor-specific antibodies was doubled in patients converting from CsA to EVL compared to patients continuing CsA (23 vs 11%)[45].

Concerning observational study on large registries, a U.S. registry study on 32604 KTR (5687 SRL exposed)[5] did not find a difference in cancer incidence in KTR on SRL (excluding non-melanoma skin cancer), and an increase incidence of prostate cancer, although there was a trend towards a beneficial effect of SRL for most other cancer types with a relative decrease in cancer incidence 26% overall[5]. The authors concluded that this modest association did not provide strong evidence that SRL prevents post-transplant cancer, but it may be advantageous among kidney recipients with high cancer risk[5]. Finally, a recent worldwide registry analysis by the Collaborative Transplant Study (CTS) group on 78146 KTRs (4279 on mTORi) again indicated that inclusion of an mTORi in the *de novo* immunosuppressive regimen had no significant influence on the incidence of post-transplant cancers other than basocellular carcinoma of the skin[42]. Studies specifically looking at the impact of mTORi on the recurrence of post-transplant cancer, however, are lacking.

PTLD. Despite in vitro evidence on mTORi inhibiting Epstein-Barr virus replication[46], the current clinical evidence on the benefit of CNI-free mTORi regimen is limited to case reports, with may suffer from publication bias. Therefore, currently, there is no evidence that allows to universally recommend a switch to a CNI-free mTORi regimens in KTRs treated for PTLD with a curative intent.

Should we switch to an immunosuppressive regimen with mTORi and low-dose CNI?

Maintenance regimens using mTORi together with CNI as opposed to CNI-free mTORi based regimens are increasingly popular, especially in KTRs, since the recent publication of the results from TRANSFORM[39,47] and ATHENA trial[48]. Compared to CNI-free mTORi based regimens, CNI+mTORi regimens appear to be more effective in preventing rejection and to be better tolerated. The TRANSFORM study[39,47] included 2037 *de novo* KTR who were randomized to a maintenance regimen including EVL and reduced-dose CNI ((EVL [target 5.5 ng/mL]+ low dose CNI [target Tac: 4ng/mL; target CsA: 50ng/mL])[39] *versus* classical CNI with MMF. After 24 months, the arm receiving EVL plus low-dose CNI showed similar results in the composite end point (which included patient and graft survival, biopsy-proven acute rejection, and glomerular filtration rate [eGFR] <50 mL/min per 1.73 m2), similar graft function, similar rates of acute rejection, and reduced incidence of CMV (7 vs 15%) and of BKV infection (4 vs 13%)[49]. Drug discontinuation was higher in EVL plus low-dose CNI (23 vs 12%), possibly due side effects such as, first and foremost, peripheral edema (37 vs 26%)[49]. Additional side effects which are more common with EVL and that may have affected the increased rate of drug discontinuation were hyperlipidemia (35 vs 19%), proteinuria (13 vs 6%), stomatitis/mouth ulcers (8 vs 2%), thrombocytopenia (7 vs 4%), and interstitial lung disease (1.1 vs 0.3%)[49]. No difference in cancer risk was detected in this study, but it is likely that longer follow-up is required to adequately assess this in the TRANSFORM study. The cancer risk was examined by a recent meta-analysis of 7356 participants from 24 RCTs[50], comparing KTRs receiving mTORi + CNI to regimens containing MMF/MPA or azathioprine (AZA) with CNI, which found a 50% decreased risk of cancer in mTORi-CNI compared to MPA/MMF/AZA-CNI at long-term follow-up (>2 y; 1466 participants). As underlined by the Authors, this effect was mainly driven by two studies[51,52]. Analyzing data of Australian and New Zealand patients from one of those two studies (A2309), and using the ANZDATA Registry to track patients in the long term, Lim *et al* [53] compared the seven-year risk of incident cancer among KTRs randomized in Australia and New Zealand to mTORi-CNI (two CsA-associated EVL dosage regimens that were pooled namely, the 1.5 mg [n = 35] and 3.0 mg [n = 31] daily, and that were compared with MMF/MPA and standard exposure CsA [n = 29]). Albeit not statistically significant because of the small sample size, the relative reduction of the incidence of non- skin cancer was 65% (hazard ratio: 0.35; 95% confidence interval: 0.09 to 1.25), the point estimate of the hazard ratio being virtually identical to the one of non-melanoma skin cancer which was significant because of the larger number of events (hazard ratio: 0.34; 95% confidence interval: 0.13 to 0.91). Interestingly, however, the effect was apparently manly driven by the 3.0mg daily regimen only (Figure 2 of the paper), which, in association with CsA, is known to correspond to an average blood trough EVL level of approximately 8 ng/mL[54] (as opposed to the 5.5 ng/mL of the 1.5 daily regimen, the same target level achieved in the TRANSFORM study)[39]. Also in the Australia and New Zealand

substudy[53], mTORi-CNI therapy was less tolerated compared to MPA/MMF. In fact, retention to original therapy beyond 2 years was 54%, and 55%, and 83%, in those allocated to EVL 1.5 mg, EVL 3 mg and MPA/MMF, respectively.

Most of the RCTs on mTORi mentioned above concern *de novo* KTRs. The evidence on the switch from CNI to mTORi comes from RCTs on non-cancer KTRs or from RCTs on KTRs with squamous cell carcinoma. The evidence on the switch from MMF/MPA to mTORi, however, is scarce. Indirect relevant evidence comes from the HERAKLES study[55,56] in which the rate of reported discontinuation due to adverse events was similar, after 4 years follow-up, in 161 CsA treated patients who switched 3 month post-transplant from MMF/MPA to EVL (target 3-8ng/mL), compared to the 165 who continued the standard CsA + MMF/MPA regimes[56]. Details on individual adverse effects have not been reported.

It is unclear whether the available evidence on the safety and efficacy of switching to an mTORi-based regime may be applied to KTRs with history of cancer that has been treated with curative intent. In the latter category of patients, the efficacy may depend on the residual tumoral burden, similarly to what have been shown with skin cancer[57]. In fact, in a RCT on squamous cell carcinoma, switching from CNI to mTOR-inhibitors halved the risk of cancer recurrence in KTRs with history of squamous cell carcinoma (from 66 to 34%)[57]. However, the effect of mTOR-inhibitors could not be demonstrated in the subgroup of patients with extensive disease (i.e. more than one tumor)[57].

The risk of rejection associated to the switch of a different immunosuppressive maintenance regimen is likely to differ according to the immunological risk profile of the patients. For instance, in solid organ transplant recipients in whom immunosuppression was reduced or withdrawn because of treatment with checkpoint inhibitors, the rejection risk varied strikingly, depending on whether that patients had a previous history of rejection and whether the elapsed time since transplant was less than 8 years (approximately ten-fold increase for each risk factor)[58]. Additionally, other well known risk factors for graft loss may affect the risk of rejection, such as re-transplantation, highly HLA mismatched organs, circulating donor specific antibodies, and life expectancy (the younger the patient's age the higher the lifetime risk of rejection). For these reasons, we contend that the preference of patients should be taken into account. In this regard, it is worth mentioning the SONG-Tx initiative[59] on kidney transplantation which was aimed at selecting the outcomes that were critically important to all stakeholders for decision making including patients and caregivers. Graft function was more important than death for patients[60]. Patients regarded death as inevitable and an ongoing risk even if they did not want to die. Ultimately, death could not be prevented, whereas, efforts could be made to prevent graft failure. Some regarded graft failure and return to dialysis to being even worse than death.

PTLD. Despite in vitro evidence on mTORi inhibiting Epstein-Barr virus replication[46], currently there is no clinical evidence of the benefit of switching from MMF/MPA to mTORi KTRs who have been treated for PTLD with curative intent. Indeed, in one study, in association with CNI, the incidence of PTLD was higher with mTORi compared to MMF/MPA or AZA[25].

Summary: information to guide shared decision making

Because the evidence on the risk/benefit of immunosuppression reduction and/or switch to mTORi based regimen in solid organ transplant recipients treated for non-skin cancer with curative intent is weak, we believe that the choice should be based on a shared decision making with the patient. Below we summarized the key points that we believe may be used by transplant physicians as a basis for informed decision making purposes. In addition, we provide a concise plain language summary for patients.

- *Potential benefits and risks of the strategy of reducing overall maintenance anti-rejection treatment*: Reducing overall maintenance anti-rejection treatment, to an extent that depends upon cancer type, stage, and other factors, has been the traditional approach used for transplant recipients with a history of non-skin cancer treated with a curative intent. This approach needs to be balanced carefully with the risk of allograft rejection and graft loss. Rejection may occur as a result of anti-rejection treatment reduction either as an acute event, with sudden deterioration of graft function, or, more likely, as a chronic process, with slow graft function deterioration over a period of months or years. The risk of graft rejection may vary between individuals, depending of time elapsed since transplantation (the longer the time elapsed the lower the risk), history of rejection or signs of ongoing chronic rejection, and patient age (the younger the age, the higher the lifetime risk of rejection). Reduction in trough blood levels of CNI inhibitor below the traditional lower bounds (e.g. halving the dose and/or Tac trough blood levels <5ng/mL, CsA < 100ng/mL) may be the most effective strategy to prevent cancer recurrence but also the least safe strategy to prevent rejection (it has been shown to cause +10% increased risk of acute rejection at 1 year in steroid-free regimens, even in low-risk individuals, in whom the reduction was carried out 4 to 12 month post-transplantation).
- *Potential benefits and risks of the strategy of switching from CNI to mTORi*: The strategy of replacing the CNI (Tac or CsA) with a mTORi (SRL or EVL) which has both immunosuppressive and anticancer effects, may be the most effective strategy in preventing recurrence of cancer, although the current available evidence on efficacy mainly concerns non-melanoma skin cancers and Kaposi sarcomas. RCTs on conversion from CsA to mTORi (SRL, target blood through level 8-20ng/mL) at various time point post-transplantation in non-cancer patients, have shown that the conversion from CNI to mTORi halves the risk of non-skin cancer. From studies on cancer patients it appears that the mTORi anti-cancer effect is dose-dependent. Unfortunately, the mTORi dosage that is most effective against cancer is often poorly tolerated. The studies performed on non-cancer kidney transplant recipients, in whom the mTORi dosage was in the lower bound of the potential effective dosage, showed that even at those low dosage, the conversion from CsA to sirolimus is associated with an increased risk of SRL withdrawal because of adverse effects. It must also be mentioned that in the same studies, conversion from CsA to mTORI was associated with increased mortality (up to 20% higher after four years in patients undergoing replacement of CsA with SRL). However, the increased risk of death was not confirmed by the most recent study, with five-year follow-up, on the conversion from CsA to EVL

(target 6-10ng/mL). The risk of graft failure associated with the conversion from CNI to mTORi may depend on baseline graft function: the risk of graft loss is lowest in patients with good graft function at the time of conversion (eGFR > 40 mL/min and protein-to-creatinine ratio ≤ 0.1). There is also some evidence that conversion to CNI to mTORI may be associated to an increased risk of developing chronic rejection (as suggested by the fact that the risk of developing donor-specific antibodies causing chronic rejection was increased by +10% after 5 years in one study).

- *Potential benefit and risks of the strategy of switching from CNI+MPA/MMF to CNI with mTORi*: The strategy of replacing the MMF/MPA with a mTORi (EVL target 5.5 ng/mL) while keeping the CNI (Tac or EVL) at low doses (target Tac 4ng/mL; target CsA 50ng/mL), may be safer with respect of the risk of rejection, and of adverse effects as compared to the previous strategy. Compared to regimes on the conversion between CsA and SRL, RCTs on the strategy of replacing the MMF/MPA with a mTORi showed that 1) the benefit in reducing the risk of non-skin cancer may be similar, but it is currently far less documented compared to the strategy of replacing CNI with mTORi, especially under the current low-dosage EVL regimes 2) there is no increased risk of rejection, graft loss, or mortality 3) they are better tolerated. However, they may still cause some side effects such as peripheral edema, stomatitis/mouth ulcers, hematologic complications that may lead to drug discontinuation. In the RCTS this has happened in at least one out of ten patients.

Summary for patients

You recently faced the diagnosis of cancer after kidney transplantation. Fortunately, you are now treated and potentially cured. In some situations, changing your anti-rejection therapy may help to further reduce the risk of cancer recurrence. However, the possible benefit of such change in medication should be carefully balanced against the risk of rejecting your kidney transplant.

1) **Would it be advisable to reduce or stop one of your anti-rejection drugs?**

Your immune system can help in fighting cancer. Therefore, it seems attractive to try and reduce the immunosuppressive medication that you take for your transplant, because this may allow your immune system to better prevent recurrence of your cancer. However, the possible benefit that you would get from reducing your ant-rejection drugs is very difficult to predict and varies with the type and stage of the cancer. It should, therefore, be discussed with your oncologist/hematologist. Reducing your medication may, on the other hand, increase your risk of rejection. Rejection could occur as an acute event, with sudden deterioration of kidney function, or, more likely, as a chronic process, with slow graft function decline over months or years. The risk of graft rejection may vary between individuals, depending of time elapsed since transplantation (the longer the time elapsed the lower the risk), history of rejection or signs of ongoing chronic rejection, and patient age (the younger the age, the higher the lifetime risk of rejection). Lowering the dose of tacrolimus or cyclosporine (if you take one of these) may be the most effective strategy to prevent cancer recurrence but also the least safe strategy to prevent rejection. The risks and benefits of reducing your anti-rejection drugs should be carefully balanced and discussed between you and your transplant physician.

2) **Would it be advisable to stop tacrolimus or cyclosporine (so called 'calcineurin-inhibitors') and replace this drug with everolimus or sirolimus ('mTOR-inhibitors')?**

mTOR inhibitors are drugs that have both anti-rejection and anti-cancer properties. Therefore, it seems to be an attractive option to stop tacrolimus/cyclosporine and replace it by an mTORi. Studies have shown that mTORi reduce the risk of skin cancer (and Kaposi sarcoma), but it is less well known if they can prevent (the recurrence of) other cancers. The higher the dose of mTORi, the higher the chance that it would have an anti-cancer effect, but unfortunately higher doses are also associated with more side effects, such as edema (swelling of the legs), mouth ulcers, and others. There is some concern that the switch from tacrolimus/cyclosporine to mTORi might increase the risk of acute or chronic rejection, but this risk depends on many factors and should be discussed with your transplant physician. It must also be mentioned that older studies have found that patients who switched from cyclosporine to sirolimus had a higher risk of death (up to 20 % higher after 4 years), although this was not the case in more recent study: it might be that transplant physicians are now more experienced in how to use these drugs in a safer way.

3) **Would it be advisable to use tacrolimus or cyclosporine (so called 'calcineurin-inhibitors') in combination with everolimus or sirolimus ('mTOR-inhibitors')?**

If you are using mycophenolate or azathioprine in combination with tacrolimus or cyclosporine, you could consider to stop mycophenolate/azathioprine and switch it to an mTOR-inhibitor, while maintaining a low dose of tacrolimus/cyclosporine. Recent studies suggest that such regimen might also reduce the risk of cancer, although we should acknowledge that the evidence is still weak. Such a strategy may be safer with respect to the risk of rejection and better tolerated than the previous strategy (see 2)).

What do other guidelines or consensus reports say?

It is clear from several consensus documents that reducing the overall immunosuppressive load is often considered, although the possible benefit in terms of reducing cancer recurrence should be balanced against the increased risk of rejection. In addition, some consensus documents suggest to consider switching to a mTORi- containing immunosuppressive regimen, which however may be poorly tolerated by some patients and increase the risk of rejection.

Guidelines/Consensus/Position paper	Recommendation
Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group. KDIGO clinical practice guideline for the care of kidney transplant recipients[61]. Chapter 20: Managing Cancer with Reduction of Immunosuppressive Medication	20.1: We suggest consideration be given to reducing immunosuppressive medications for kidney transplant recipients with cancer. (2C)* 20.1.1: Important factors for consideration include (Not Graded): • the stage of cancer at diagnosis; • whether the cancer is likely to be exacerbated by immunosuppression; • the therapies available for the cancer; • whether immunosuppressive medications interfere with ability to administer the standard chemotherapy. 20.2: For patients with Kaposi sarcoma, we suggest using mTORi along with a reduction in overall immunosuppression. (2C) ** Level 2 'We suggest', C 'Quality of evidence is low'*
EBPG Expert Group on Renal Transplantation. European best practice guidelines for renal transplantation. Section IV: longterm management of the transplant recipient. IV.6.3 Solid organ cancers: prevention and treatment[62]	The European Best Practice Guidelines were produced by the European Renal Association – European Dialysis Transplant Association (ERA-EDTA). The guidance states that it is recommended to reduce immunosuppression whenever possible in transplant patients who are diagnosed with cancer (Evidence level C: guidelines are derived from small or controversial studies or represent the opinion of the group of experts).
Epailly E, Albanell J, Andreassen A, et al. Proliferation signal inhibitors and post-transplant malignancies in heart transplantation: practical clinical management questions[63].	The report provides practical guidance from a collaborative group that used literature and personal clinical experience to reach consensus regarding posttransplant malignancies in heart transplant patients. The group proposes a (unvalidated) treatment algorithm that can carefully consider cancer type and patient's risk of acute rejection and can incorporate decisions with minimization or withdrawal of calcineurin inhibitors and introduction of mTORi.
Campistol JM, Albanell J, Arns W, Boletis I, Dantal J, et al. Use of proliferation signal inhibitors in the management of post-transplant malignancies—clinical guidance[64].	The paper presents guidance regarding immunosuppression for kidney transplant patients diagnosed with cancer following an industry-sponsored workshop. A recommended treatment algorithm based on clinical experience is presented suggesting to reduce or stop CNIs and start mTORi.
Małyszko J, Bamias A, Danesh FR, Dębska-Ślizień A, Gallieni M, Gertz MA, Kielstein JT, Tesarova P, Wong G, Cheung M, Wheeler DC, Winkelmayer WC, Porta C; Conference	The management of cancer after kidney transplantation is complex. For patients who develop cancer after kidney transplantation, the approach has traditionally focused on reducing overall immunosuppression, with administration of chemotherapy agents managed by a medical oncologist. Dose reduction of immunosuppression after transplantation is

Participants. KDIGO Controversies Conference on onco-nephrology: kidney disease in hematological malignancies and the burden of cancer after kidney transplantation[65].	likely to depend upon cancer type, stage, and many other factors. However, this approach needs to be balanced carefully with the risk of allograft rejection. Prospective trial-based data to inform immunosuppression management, including dose reduction and/or immunosuppression cessation, are lacking. Mammalian target of rapamycin inhibitors (sirolimus and everolimus) may have a promising role in managing cancer after transplantation (particularly with nonmelanocytic skin cancers and Kaposi sarcomas), owing to their simultaneous immunosuppressive and anticancer effects

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